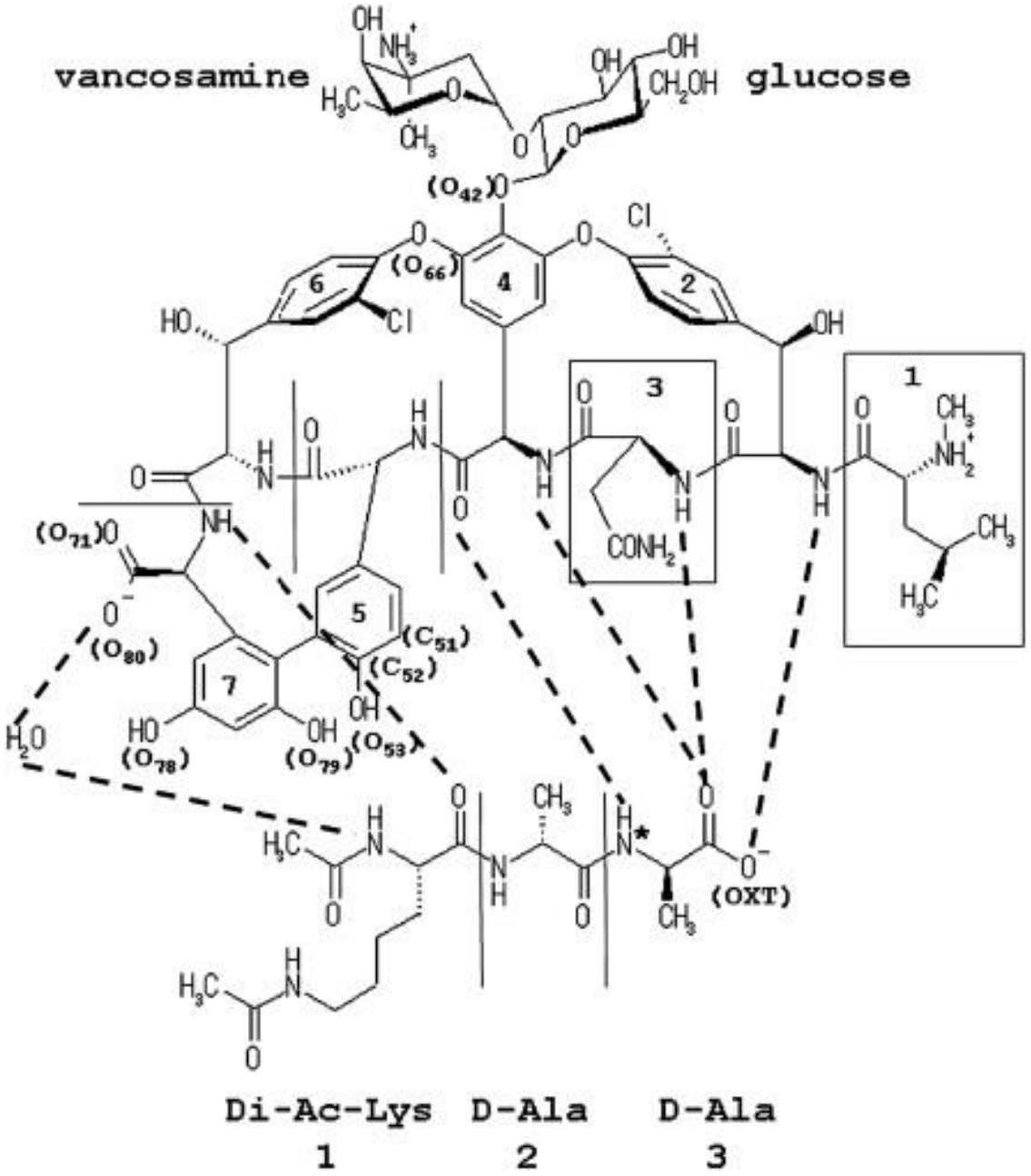
Recognition of Hydrophilic Molecules by Designed Small Molecular Receptor in Water

LITERATURE SEMINAR#2 19/07/19

Y.KAMIMURA



J. Mol. Biol., **2009**, *385*, 1422

1. Introduction

2. Analysis on molecular recognition in water

3. Case examples

    Recognition of lysine in water

    Recognition of glucose in water

4. Appendix

Introduction

- Molecular recognition

  Specific interaction between two or more molecules by non-covalent bonding.

- It is one of the most basic phenomenon in organisms.

- Understanding of it is of great importance for every fields.

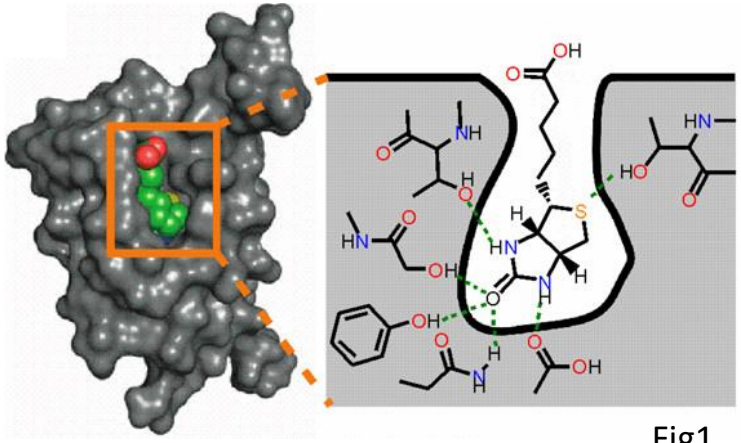


Fig1

Fig1 : *J. Am. Chem. Soc.*, **2018,** *140*, 13466

Introduction

- 1967 : Crown ether (C. J. Pdersen)
- Since then, molecular recognition has been intensively studied.
- Cyclic host molecules can be divided into 2 groups; molecules with hydrophobic cavity and molecules with polar binding site.

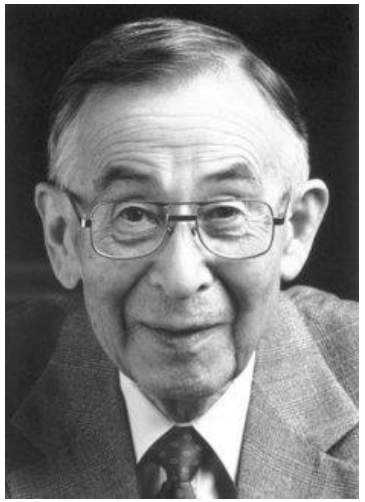
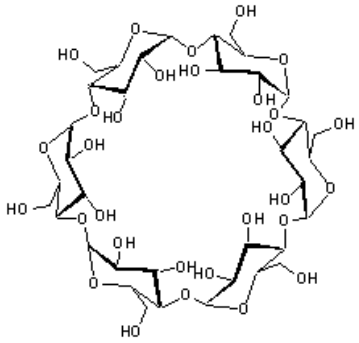
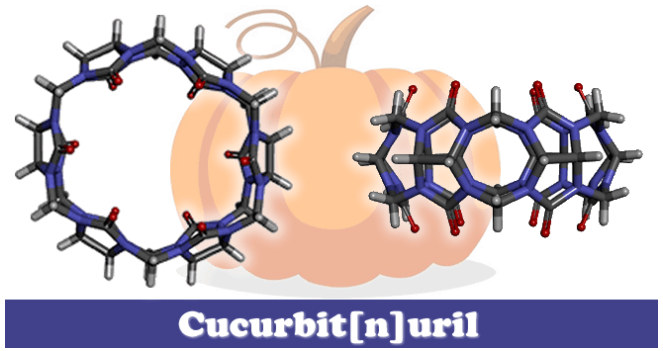
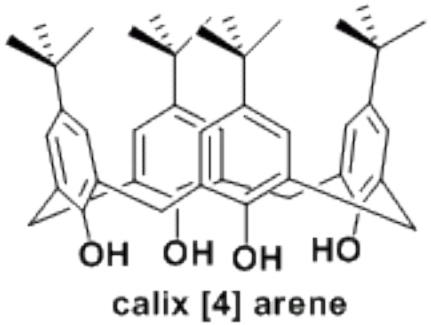
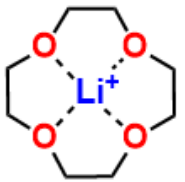


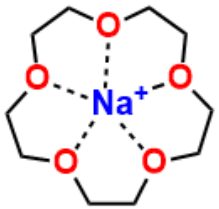
Fig1











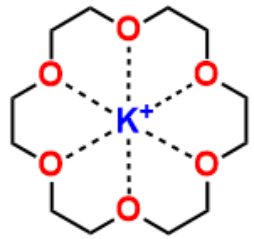
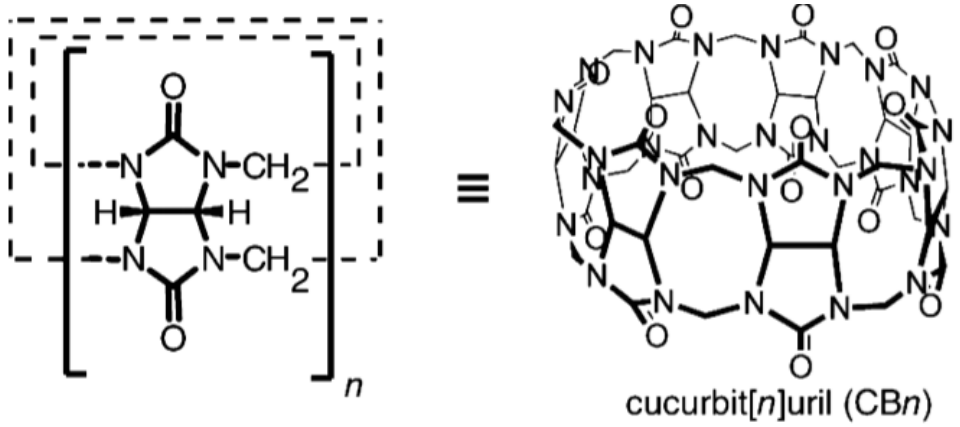


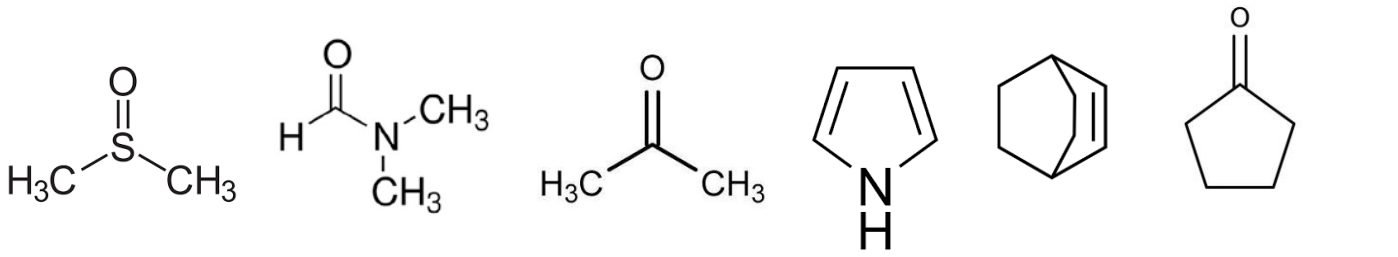
Fig2

Fig1 : https://www.nobelprize.org/prizes/chemistry/1987/pedersen/biographical/
Fig2 : https://www.chem-station.com/

Introduction

- There are some reports of molecular recognition by hydrophobic host.
- Size and shape have more effect than functional group.
- Comparing hydrophilic hosts and hydrophobic hosts, the latter are preferred.





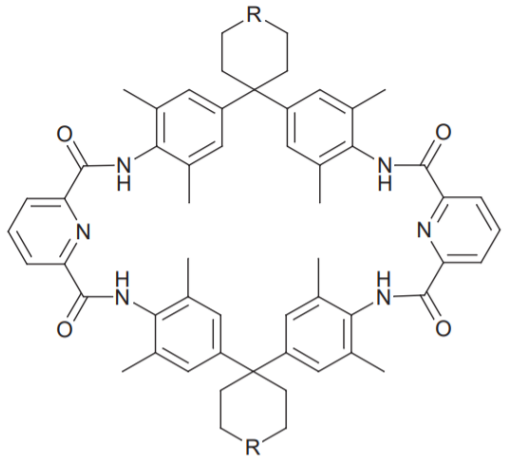
	K_a (10^3 M^{-1})	ΔH^a (kJ/mol)	$-T\Delta S^a$ (kJ/mol)
CB6·DMSO	1.2 ± 0.3	−5 ± 1	−24 ± 3
CB7·DMSO	0.13 ± 0.02	−14 ± 1	2 ± 2
CB6·DMF	1.8 ± 0.3	−6 ± 1	−24 ± 3
CB7·DMF	0.61 ± 0.02	−22 ± 1	6 ± 2
CB6·acetone	7.2 ± 0.3	−11 ± 2	−11 ± 4
CB7·acetone	0.64 ± 0.02	−13 ± 1	−1 ± 2
CB6·pyrrole	36 ± 3	−23 ± 2	−3 ± 4
CB7·pyrrole	1.7 ± 0.2	−30 ± 1	11 ± 2
CB7·DBO[f]	13400 ± 200[g]	−75 ± 1	34 ± 2
CB8·DBO[f]	16 ± 3	−37 ± 1	13 ± 3
CB7·cyclopentanone	330 ± 0.2	−41 ± 1	9 ± 2
CB8·cyclopentanone	1.1 ± 0.2	−35 ± 1	18 ± 2

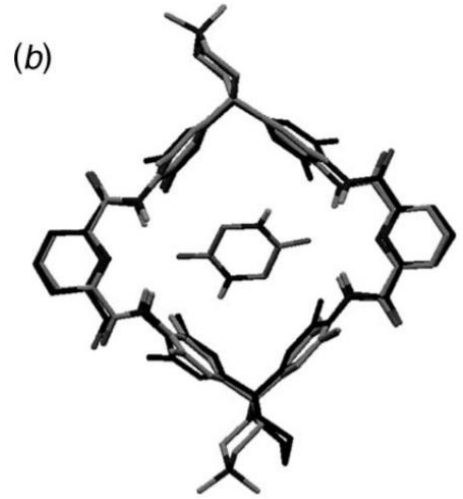
F.Biedermann et al, *J. Am. Chem. Soc.*, ***2012***, 134, 15318

Introduction

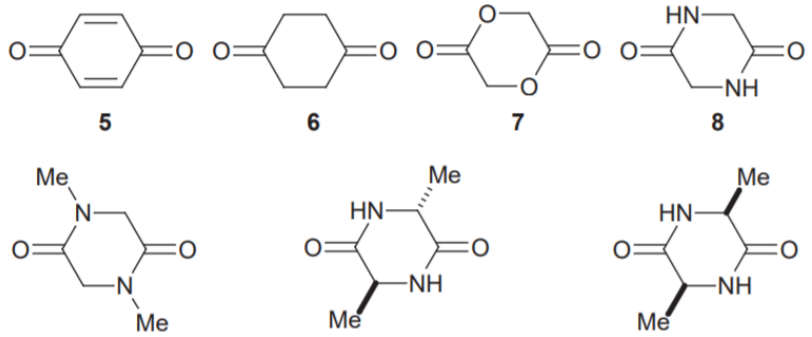
- Molecular recognition by a molecule with polar binding site is also reported.
- However, affinity is significantly attenuated in water.

8 : $K_a = 1.0 \times 10^6$ M^{-1} ($CHCl_3$) → 71 ± 8 M^{-1} (H_2O)





Host molecule



Guest molecule

C. Allott et al, *Chem. Commun.*, **1998**, 2449

1. Introduction

2. Analysis on molecular recognition in water

3. Case examples

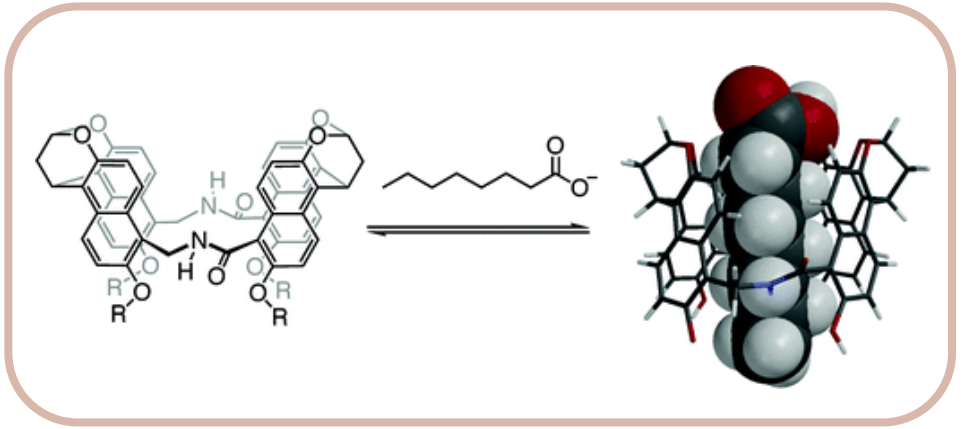
    Recognition of lysine in water

    Recognition of glucose in water

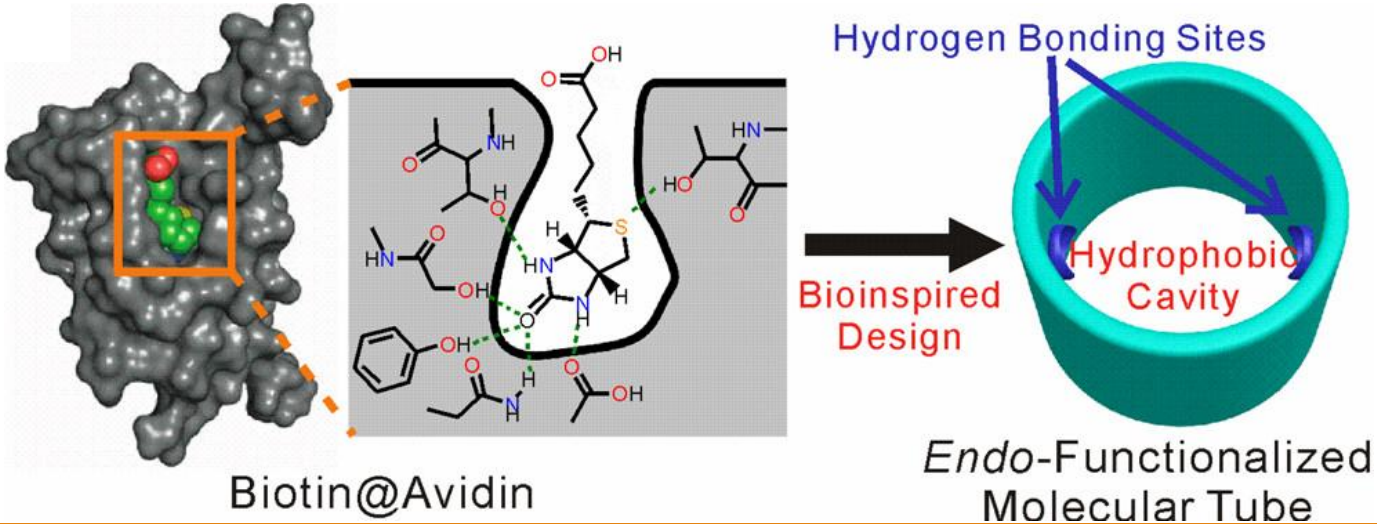
4. Appendix

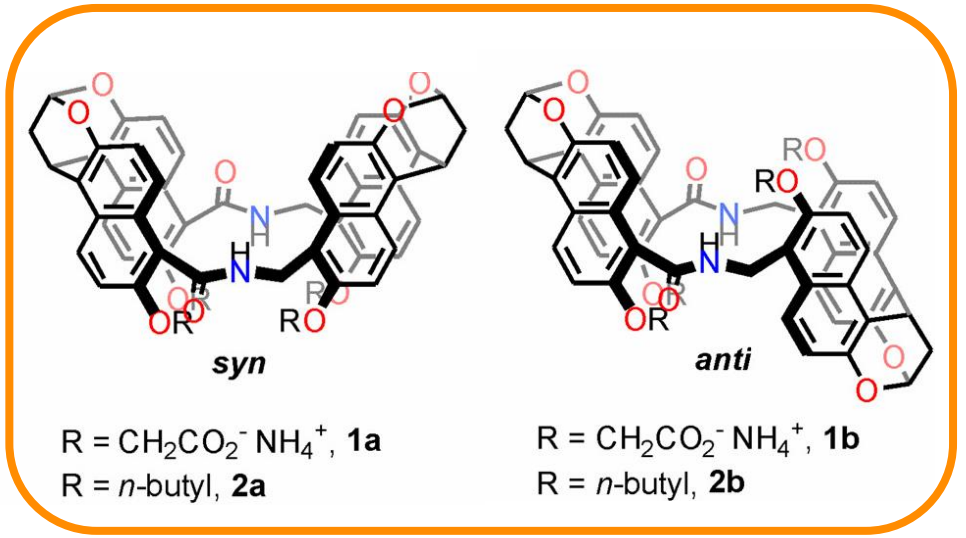
Molecular recognition in water

- Biomolecules can recognize hydrophilic molecules in water.
- They have hydrophilic recognition site in its hydrophobic cavity.
- Artificial mimic of it was conceived.



B. J. Shorthill et al., *J. Am. Chem. Soc.*, **2004**, *126*, 12732

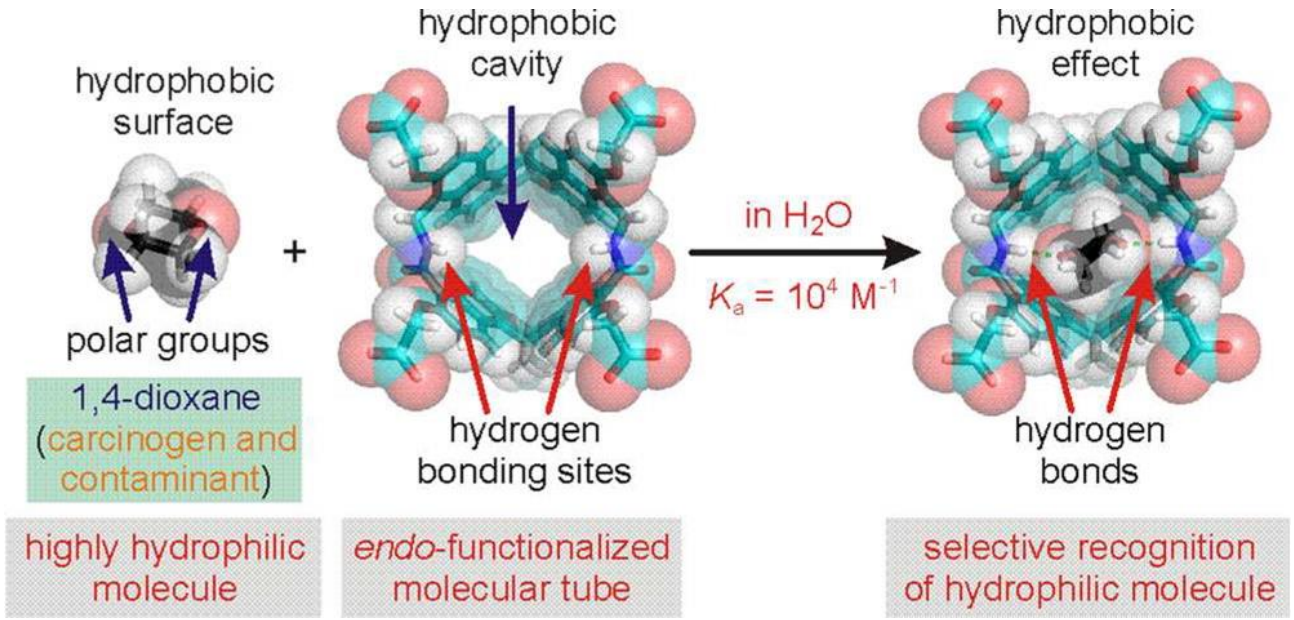




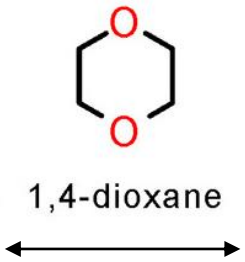
G Huang et al, *J. Am. Chem. Soc.*, **2016**, *138*, 14550.
H. Yao, et al., *J. Am. Chem. Soc.*, **2018**, *140*, 13466

Molecular recognition in water

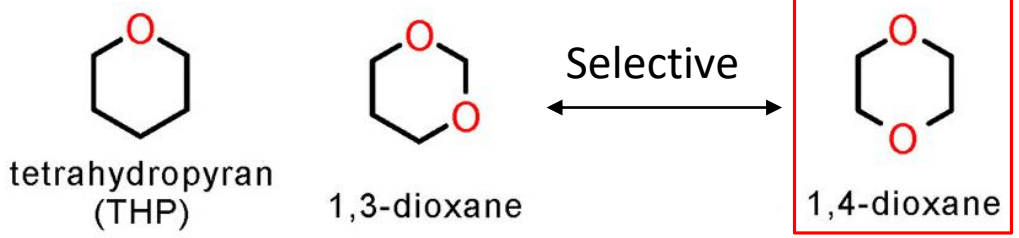
- How hydrophobic effect works in the recognition of hydrophilic molecules?
- Is CH-π interaction involved?
- How can the host distinguish between these similar molecules?



In CHCl3
$K_a = 10^2$



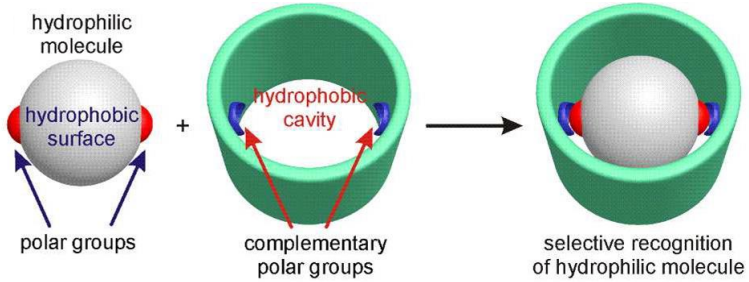
In water
$K_a = 10^4$

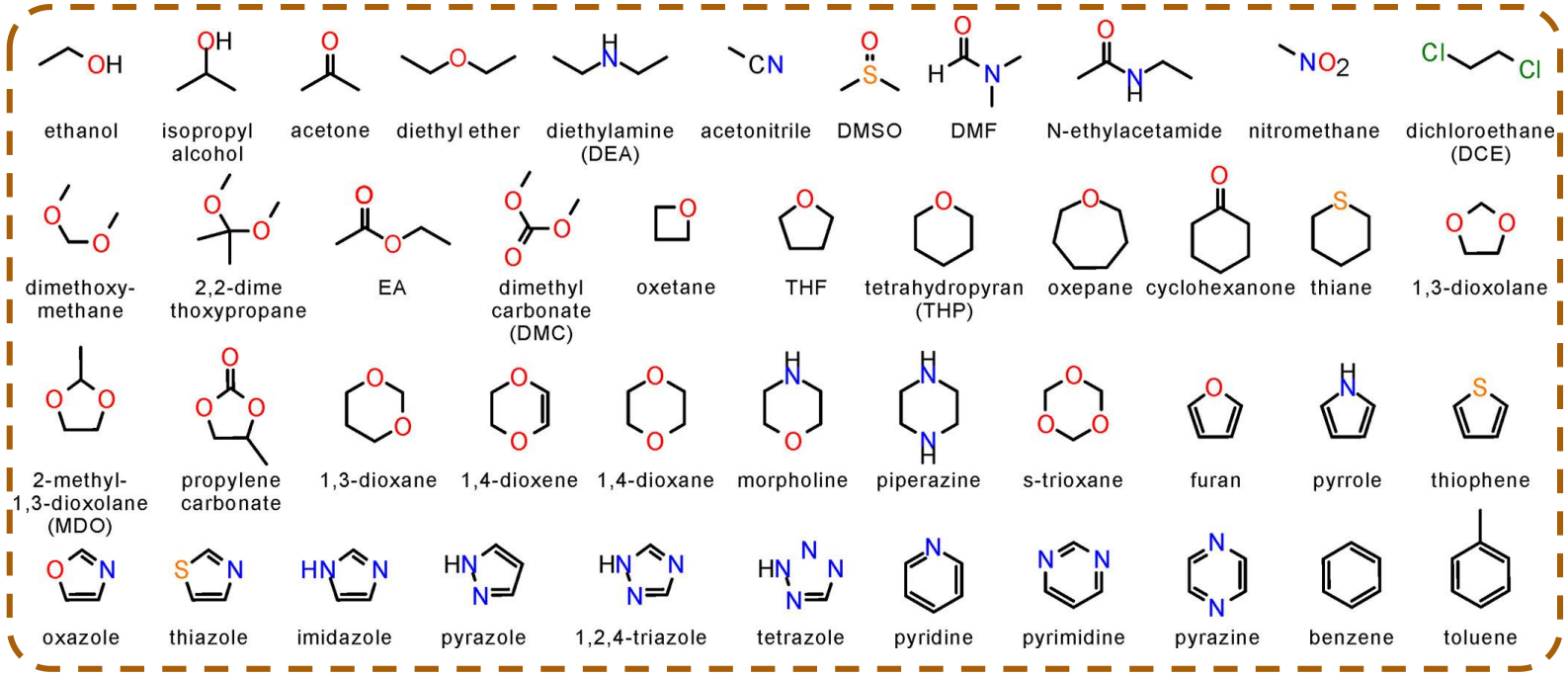


G Huang et al, *J. Am. Chem. Soc.*, **2016**, *138*, 14550.
H. Yao, et al., *J. Am. Chem. Soc.*, **2018**, *140*, 13466

Molecular recognition in water

IAuthors analyzed the complexation process, using 44 hydrophilic small molecules as hosts.





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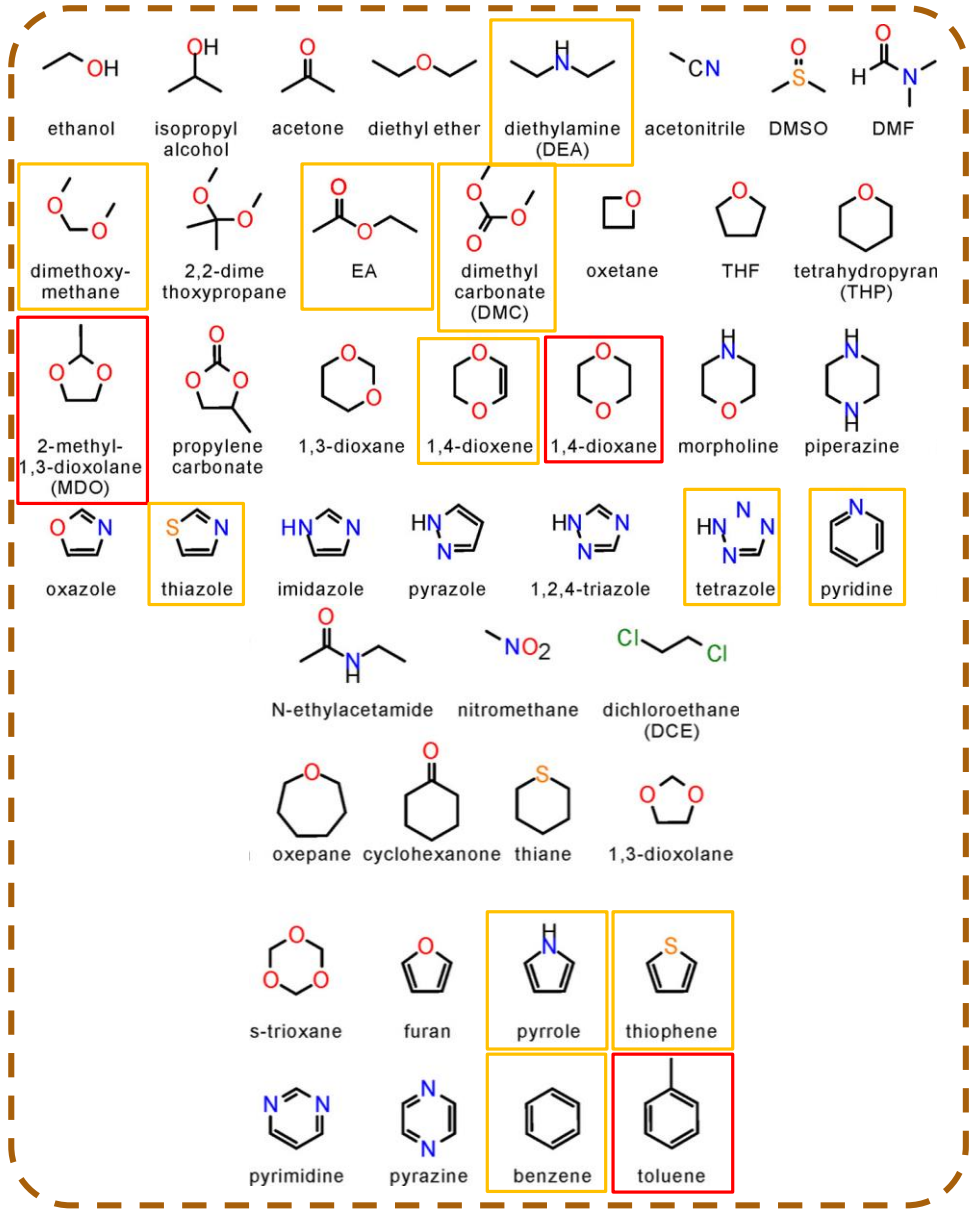
JACS, **2018,** *140*, 13466

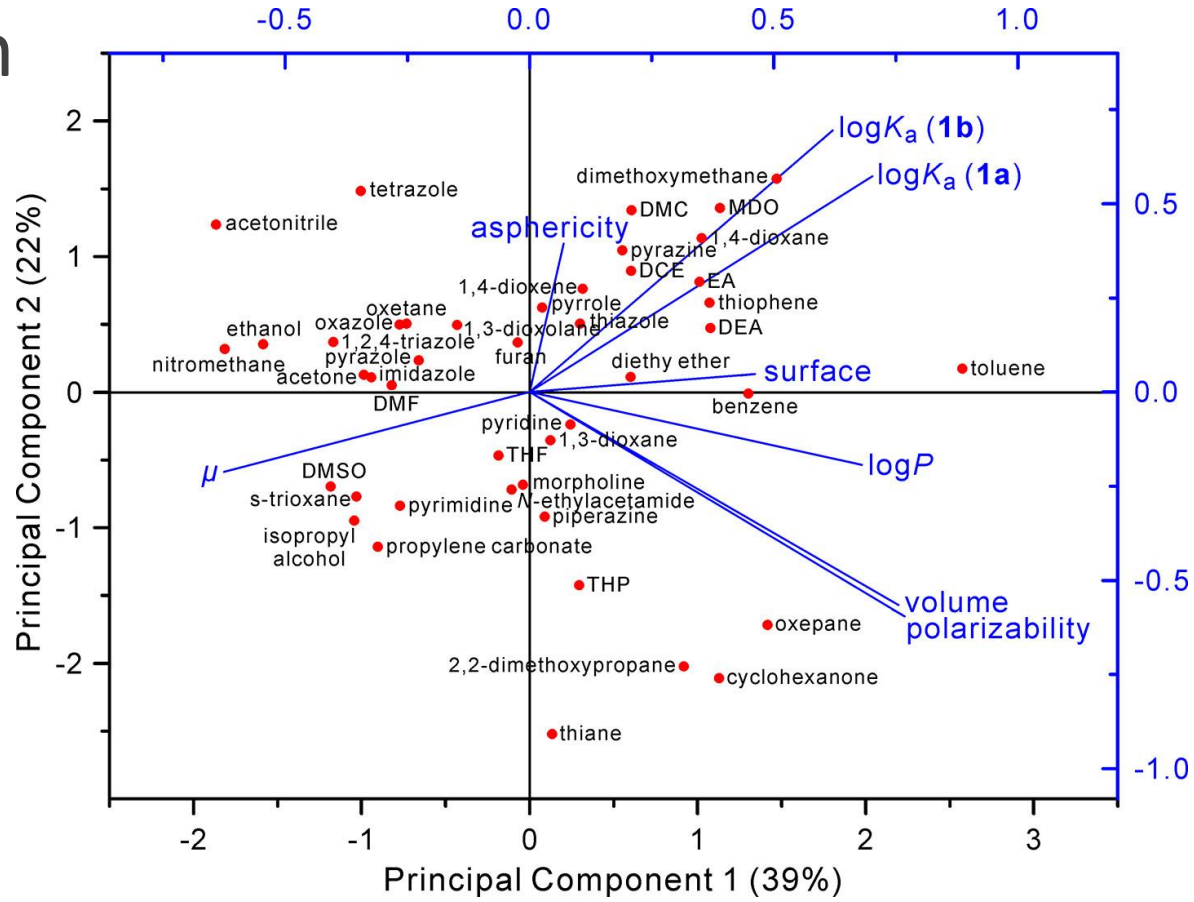
Affinity



guest	V (Å^3)[a]	Ω_A[a]	S (Å^2)[a]	S_{MAX} (M)[b]	log P[b]	μ (D)[c]	α (Bohr^3)[c]	K_a (**1a**, M^{-1})	K_a (**1b**, M^{-1})
ethanol	76.54	0.11373	93.94	misc[d]	−0.30	1.88	25.95	9 ± 2[h]	43 ± 13[h]
isopropyl alcohol	100.13	0.03907	113.95	misc	0.05	1.89	36.36	9 ± 4[h]	20 ± 5[h]
acetone[e]	91.26	0.05329	107.99	misc	−0.24	3.09	33.22	100 ± 10	110 ± 10
diethy ether	123.58	0.17298	139.41	8.15×10^{-1}	0.89	1.38	48.28	290 ± 39[h]	330 ± 88[h]
DEA[f]	129.91	0.17562	142.89	misc	0.58	0.48	50.89	1500 ± 120[i]	460 ± 11[i]
acetonitrile	68.73	0.20998	85.62	misc	−0.34	3.88	22.47	8 ± 3[h]	160 ± 43[h]
DMSO[e]	102.16	0.03143	116.48	misc	−1.35	4.92	44.68	31 ± 4	130 ± 10
DMF[e]	105.78	0.08156	121.33	misc	−1.01	4.44	40.52	310 ± 31	120 ± 12
N-ethylacetamide	130.92	0.13133	144.55	1.32[g]	−0.19[g]	4.10	50.95	65 ± 10[h]	150 ± 25[h]
nitromethane	74.53	0.05675	91.54	1.82	−0.33	3.85	24.39	17 ± 8[h]	110 ± 2[h]
DCE	107.87	0.21466	121.44	8.61×10^{-2}	1.48	0.00	40.64	270 ± 23[j]	400 ± 21[j]
dimethoxymethane	113.25	0.08744	445.61	3.02×10^{-1}	0.00	2.38	40.67	6700 ± 140[i]	5200 ± 590[i]
2,2-dimethoxypropane	152.34	0.02584	157.50	7.22×10^{-2}	1.38	2.30	60.81	49 ± 13[h]	140 ± 3[h]
EA	125.99	0.12646	140.88	9.08×10^{-1}	0.73	1.94	47.95	3400 ± 24[i]	2300 ± 140[i]
DMC	114.94	0.13347	128.20	9.44×10^{-1}[g]	0.07[g]	0.11	40.37	2300 ± 110[i]	1400 ± 52[i]
oxetane[e]	88.20	0.04207	102.57	misc	−0.14	2.50	32.72	300 ± 30	240 ± 25
THF[e]	107.45	0.04022	119.52	misc	0.46	2.26	43.16	230 ± 25	90 ± 10
THP[e]	127.01	0.04092	135.38	9.31×10^{-1}	0.82	1.83	53.97	68 ± 7	60 ± 6
oxepane[e]	148.63	0.03939	151.49	2.68×10^{-2}	1.92	1.70	64.13	380 ± 40	150 ± 20
cyclohexanone	140.93	0.06941	147.72	2.34×10^{-1}	0.81	3.42	61.31	35 ± 5[h]	6 ± 1[h]
thiane	140.33	0.04774	146.85	1.27×10^{-2}	2.28	2.37	65.96	65 ± 6[h]	120 ± 9[h]
1,3-dioxolane	96.85	0.04306	109.98	3.74	−0.37	1.48	36.21	430 ± 39[i]	260 ± 5[i]
MDO	117.76	0.06975	131.51	7.94×10^{-1}[g]	0.08[g]	1.35	46.61	2000 ± 730[i]	8100 ± 79[i]
propylene carbonate	119.00	0.06329	133.46	1.71	−0.41	6.16	47.59	51 ± 5[i]	62 ± 5[i]
1,3-dioxane[e]	115.90	0.04233	126.15	9.94×10^{-1}	0.18	1.44	46.19	210 ± 21	210 ± 21
1,4-dioxene	106.94	0.04980	120.68	misc[g]	−0.39[g]	0.95	43.75	1800 ± 73[i]	1000 ± 76[i]
1,4-dioxane[e]	116.07	0.04253	126.70	misc	−0.27	0.00	47.23	4000 ± 1500	3200 ± 300
morpholine[f]	124.32	0.04235	130.78	misc	−0.86	2.01	50.72	190 ± 8[i]	130 ± 6[i]
piperazine[f]	130.42	0.04224	134.82	misc	−1.50	0.00	54.09	210 ± 17[i]	40 ± 3[i]
s-trioxane	104.50	0.04396	116.30	1.94	−0.43	2.65	38.87	47 ± 3[h]	17 ± 8[h]
furan	93.86	0.06254	105.94	1.47×10^{-1}	1.34	1.08	36.05	490 ± 23[i]	150 ± 20[i]
pyrrole	97.36	0.06252	110.46	7.01×10^{-1}	0.75	1.90	39.68	1500 ± 59[i]	390 ± 2[i]
thiophene	107.02	0.06994	117.95	3.59×10^{-2}	1.81	1.02	49.12	4000 ± 230[i]	2100 ± 200[i]
oxazole	85.54	0.06260	100.66	1.55	0.12	1.53	32.51	130 ± 22[i]	130 ± 10[i]
thiazole	101.76	0.07153	113.00	6.32×10^{-1}	0.44	1.32	45.91	1400 ± 220[i]	420 ± 14[i]
imidazole	91.92	0.06258	105.26	2.34	−0.08	3.97	36.16	330 ± 33[h]	69 ± 13[h]
pyrazole	91.76	0.06252	105.34	1.20	0.26	2.47	36.10	180 ± 9[i]	130 ± 14[i]
1,2,4-triazole	85.74	0.06259	100.03	6.14	−0.58	2.99	32.49	210 ± 21[i]	61 ± 14[i]
tetrazole	83.11	0.06255	95.43	3.08×10^{-1}	−0.60	5.77	29.72	1800 ± 650[i]	2100 ± 350[i]
pyridine	111.97	0.06257	122.09	misc	0.65	2.48	49.41	590 ± 48[i]	220 ± 29[i]
pyrimidine	105.06	0.06255	117.14	3.58	−0.40	2.61	45.33	62 ± 5[i]	18 ± 4[i]
pyrazine	104.15	0.06280	117.32	2.72	−0.26	0.00	45.97	2200 ± 38[i]	1900 ± 100[i]
benzene	116.30	0.06250	126.89	2.29×10^{-2}	2.13	0.00	53.33	1300 ± 190[i]	750 ± 69[i]
toluene	141.22	0.08711	147.37	5.71×10^{-3}	2.73	0.36	65.49	9500 ± 1700[i]	9900 ± 1400

PCA

- Dipole moment has medium degree of negative correlation with the binding affinity.
- LogP, surface area, polarizability, volume have weak positive correlation.
- However none of the parameters is sufficient for the explanation of the affinity.



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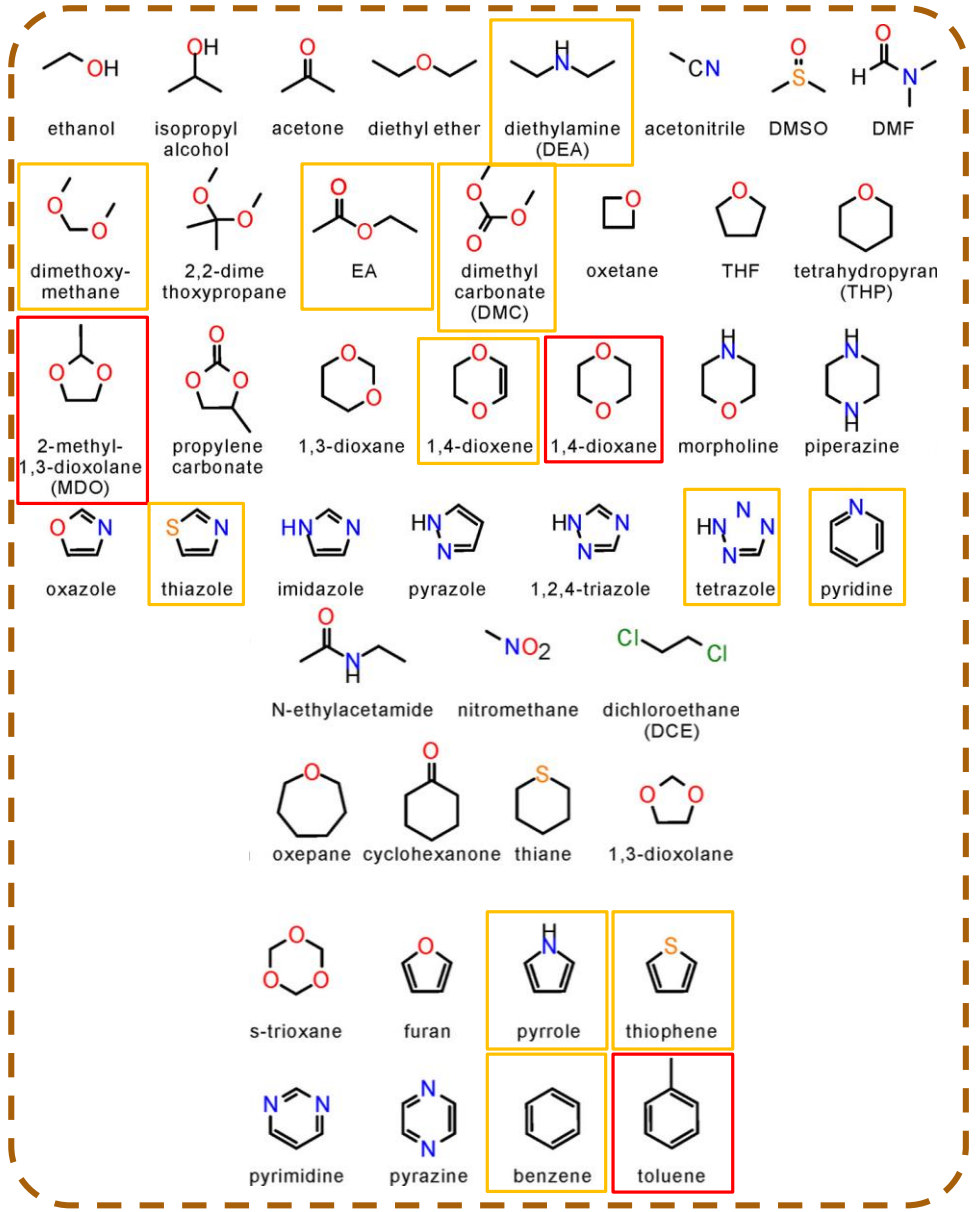
Dipole moment



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acetonitrile	68.73	0.20998	85.62	misc	−0.34	3.88	22.47	8 ± 3[h]	160 ± 43[h]
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DCE	107.87	0.21466	121.44	8.61×10^{-2}	1.48	0.00	40.64	270 ± 23[j]	400 ± 21[j]
dimethoxymethane	113.25	0.08744	445.61	3.02×10^{-1}	0.00	2.38	40.67	6700 ± 140[i]	5200 ± 590[i]
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EA	125.99	0.12646	140.88	9.08×10^{-1}	0.73	1.94	47.95	3400 ± 24[i]	2300 ± 140[i]
DMC	114.94	0.13347	128.20	9.44×10^{-1}[g]	0.07[g]	0.11	40.37	2300 ± 110[i]	1400 ± 52[i]
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thiane	140.33	0.04774	146.85	1.27×10^{-2}	2.28	2.37	65.96	65 ± 6[h]	120 ± 9[h]
1,3-dioxolane	96.85	0.04306	109.98	3.74	−0.37	1.48	36.21	430 ± 39[i]	260 ± 5[i]
MDO	117.76	0.06975	131.51	7.94×10^{-1}[g]	0.08[g]	1.35	46.61	22000 ± 730[i]	8100 ± 79[i]
propylene carbonate	119.00	0.06329	133.46	1.71	−0.41	6.16	47.59	51 ± 5[i]	62 ± 5[i]
1,3-dioxane[e]	115.90	0.04233	126.15	9.94×10^{-1}	0.18	1.44	46.19	210 ± 21	210 ± 21
1,4-dioxene	106.94	0.04980	120.68	misc[g]	−0.39[g]	0.95	43.75	1800 ± 73[i]	1000 ± 76[i]
1,4-dioxane[e]	116.07	0.04253	126.70	misc	−0.27	0.00	47.23	14000 ± 1500	3200 ± 300
morpholine[f]	124.32	0.04235	130.78	misc	−0.86	2.01	50.72	190 ± 8[i]	130 ± 6[i]
piperazine[f]	130.42	0.04224	134.82	misc	−1.50	0.00	54.09	210 ± 17[i]	40 ± 3[i]
s-trioxane	104.50	0.04396	116.30	1.94	−0.43	2.65	38.87	47 ± 3[h]	17 ± 8[h]
furan	93.86	0.06254	105.94	1.47×10^{-1}	1.34	1.08	36.05	490 ± 23[i]	150 ± 20[i]
pyrrole	97.36	0.06252	110.46	7.01×10^{-1}	0.75	1.90	39.68	1500 ± 59[i]	390 ± 2[i]
thiophene	107.02	0.06994	117.95	3.59×10^{-2}	1.81	1.02	49.12	4000 ± 230[i]	2100 ± 200[i]
oxazole	85.54	0.06260	100.66	1.55	0.12	1.53	32.51	130 ± 22[i]	130 ± 10[i]
thiazole	101.76	0.07153	113.00	6.32×10^{-1}	0.44	1.32	45.91	1400 ± 220[i]	420 ± 14[i]
imidazole	91.92	0.06258	105.26	2.34	−0.08	3.97	36.16	330 ± 33[h]	69 ± 13[h]
pyrazole	91.76	0.06252	105.34	1.20	0.26	2.47	36.10	180 ± 9[i]	130 ± 14[i]
1,2,4-triazole	85.74	0.06259	100.03	6.14	−0.58	2.99	32.49	210 ± 21[i]	61 ± 14[i]
tetrazole	83.11	0.06255	95.43	3.08×10^{-1}	−0.60	5.77	29.72	1800 ± 650[i]	2100 ± 350[i]
pyridine	111.97	0.06257	122.09	misc	0.65	2.48	49.41	590 ± 48[i]	220 ± 29[i]
pyrimidine	105.06	0.06255	117.14	3.58	−0.40	2.61	45.33	62 ± 5[i]	18 ± 4[i]
pyrazine	104.15	0.06280	117.32	2.72	−0.26	0.00	45.97	2200 ± 38[i]	1900 ± 100[i]
benzene	116.30	0.06250	126.89	2.29×10^{-2}	2.13	0.00	53.33	1300 ± 190[i]	750 ± 69[i]
toluene	141.22	0.08711	147.37	5.71×10^{-3}	2.73	0.36	65.49	9500 ± 1700[i]	9900 ± 1400

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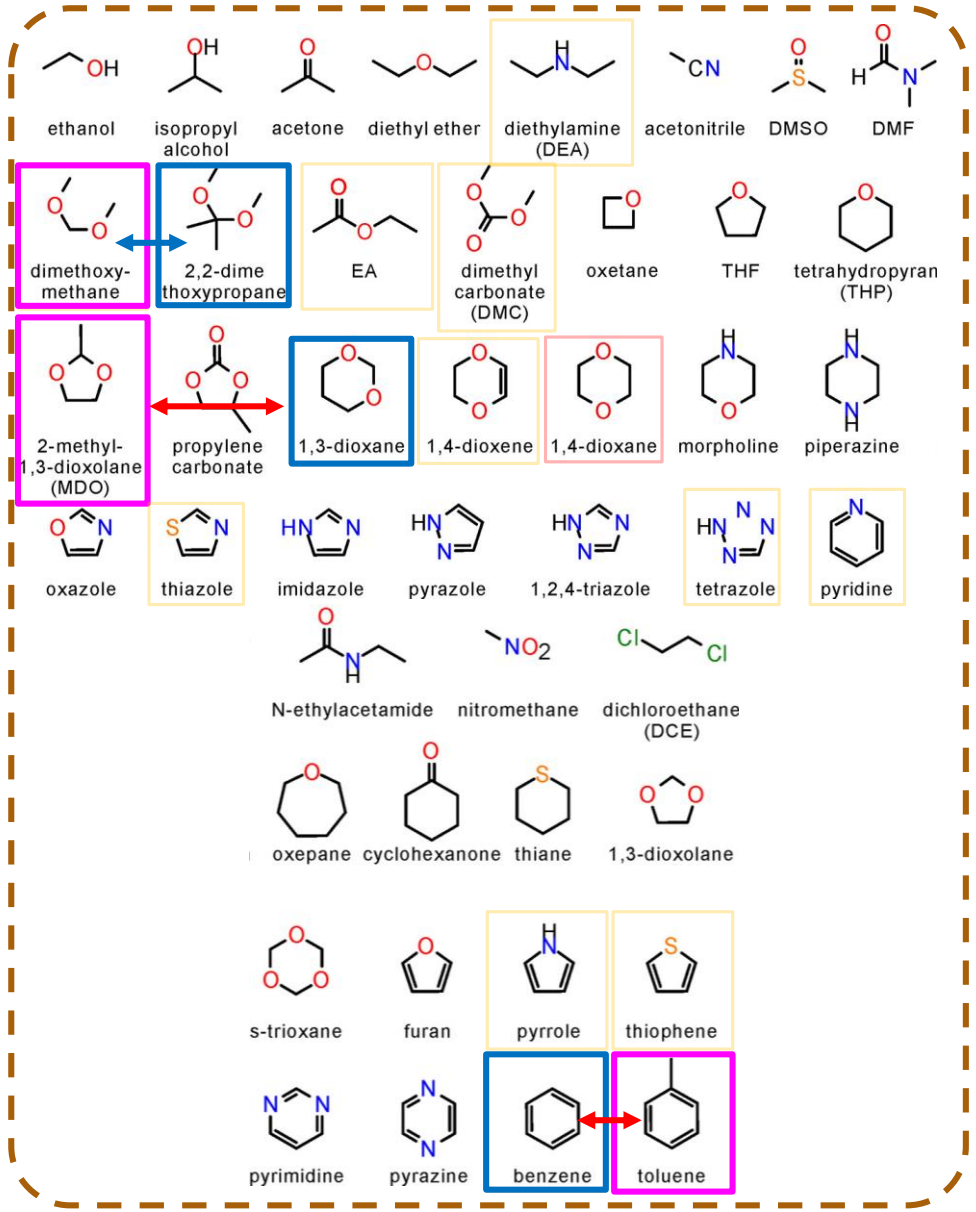
Effect of hydrophobic group



guest	V (Å^3)[a]	Ω_A[a]	S (Å^2)[a]	S_{MAX} (M)[b]	log P[b]	μ (D)[c]	α (Bohr^3)[c]	K_a (**1a**, M^{-1})	K_a (**1b**, M^{-1})
ethanol	76.54	0.11373	93.94	misc[d]	−0.30	1.88	25.95	9 ± 2[h]	43 ± 13[h]
isopropyl alcohol	100.13	0.03907	113.95	misc	0.05	1.89	36.36	9 ± 4[h]	20 ± 5[h]
acetone[e]	91.26	0.05329	107.99	misc	−0.24	3.09	33.22	100 ± 10	110 ± 10
diethy ether	123.58	0.17298	139.41	8.15×10^{-1}	0.89	1.38	48.28	290 ± 39[h]	330 ± 88[h]
DEA[f]	129.91	0.17562	142.89	misc	0.58	0.48	50.89	1500 ± 120[i]	460 ± 11[i]
acetonitrile	68.73	0.20998	85.62	misc	−0.34	3.88	22.47	8 ± 3[h]	160 ± 43[h]
DMSO[e]	102.16	0.03143	116.48	misc	−1.35	4.92	44.68	31 ± 4	130 ± 10
DMF[e]	105.78	0.08156	121.33	misc	−1.01	4.44	40.52	310 ± 31	120 ± 12
N-ethylacetamide	130.92	0.13133	144.55	1.32[g]	−0.19[g]	4.10	50.95	65 ± 10[h]	150 ± 25[h]
nitromethane	74.53	0.05675	91.54	1.82	−0.33	3.85	24.39	17 ± 8[h]	110 ± 2[h]
DCE	107.87	0.21466	121.44	8.61×10^{-2}	1.48	0.00	40.64	270 ± 23[j]	400 ± 21[j]
dimethoxymethane	113.25	0.08744	445.61	3.02×10^{-1}	0.00	2.38	40.67	6700 ± 140[i]	5200 ± 590[i]
2,2-dimethoxypropane	152.34	0.02584	157.50	7.22×10^{-2}	1.38	2.30	60.81	49 ± 13[h]	140 ± 3[h]
EA	125.99	0.12646	140.88	9.08×10^{-1}	0.73	1.94	47.95	3400 ± 24[i]	2300 ± 140[i]
DMC	114.94	0.13347	128.20	9.44×10^{-1}[g]	0.07[g]	0.11	40.37	2300 ± 110[i]	1400 ± 52[i]
oxetane[e]	88.20	0.04207	102.57	misc	−0.14	2.50	32.72	300 ± 30	240 ± 25
THF[e]	107.45	0.04022	119.52	misc	0.46	2.26	43.16	230 ± 25	90 ± 10
THP[e]	127.01	0.04092	135.38	9.31×10^{-1}	0.82	1.83	53.97	68 ± 7	60 ± 6
oxepane[e]	148.63	0.03939	151.49	2.68×10^{-2}	1.92	1.70	64.13	380 ± 40	150 ± 20
cyclohexanone	140.93	0.06941	147.72	2.34×10^{-1}	0.81	3.42	61.31	35 ± 5[h]	6 ± 1[h]
thiane	140.33	0.04774	146.85	1.27×10^{-2}	2.28	2.37	65.96	65 ± 6[h]	120 ± 9[h]
1,3-dioxolane	96.85	0.04306	109.98	3.74	−0.37	1.48	36.21	430 ± 39[i]	260 ± 5[i]
MDO	117.76	0.06975	131.51	7.94×10^{-1}[g]	0.08[g]	1.35	46.61	22000 ± 730[i]	8100 ± 79[i]
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oxazole	85.54	0.06260	100.66	1.55	0.12	1.53	32.51	130 ± 22[i]	130 ± 10[i]
thiazole	101.76	0.07153	113.00	6.32×10^{-1}	0.44	1.32	45.91	1400 ± 220[i]	420 ± 14[i]
imidazole	91.92	0.06258	105.26	2.34	−0.08	3.97	36.16	330 ± 33[h]	69 ± 13[h]
pyrazole	91.76	0.06252	105.34	1.20	0.26	2.47	36.10	180 ± 9[i]	130 ± 14[i]
1,2,4-triazole	85.74	0.06259	100.03	6.14	−0.58	2.99	32.49	210 ± 21[i]	61 ± 14[i]
tetrazole	83.11	0.06255	95.43	3.08×10^{-1}	−0.60	5.77	29.72	1800 ± 650[j]	2100 ± 350[j]
pyridine	111.97	0.06257	122.09	misc	0.65	2.48	49.41	590 ± 48[i]	220 ± 29[i]
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toluene	141.22	0.08711	147.37	5.71×10^{-3}	2.73	0.36	65.49	9500 ± 1700[i]	9900 ± 1400

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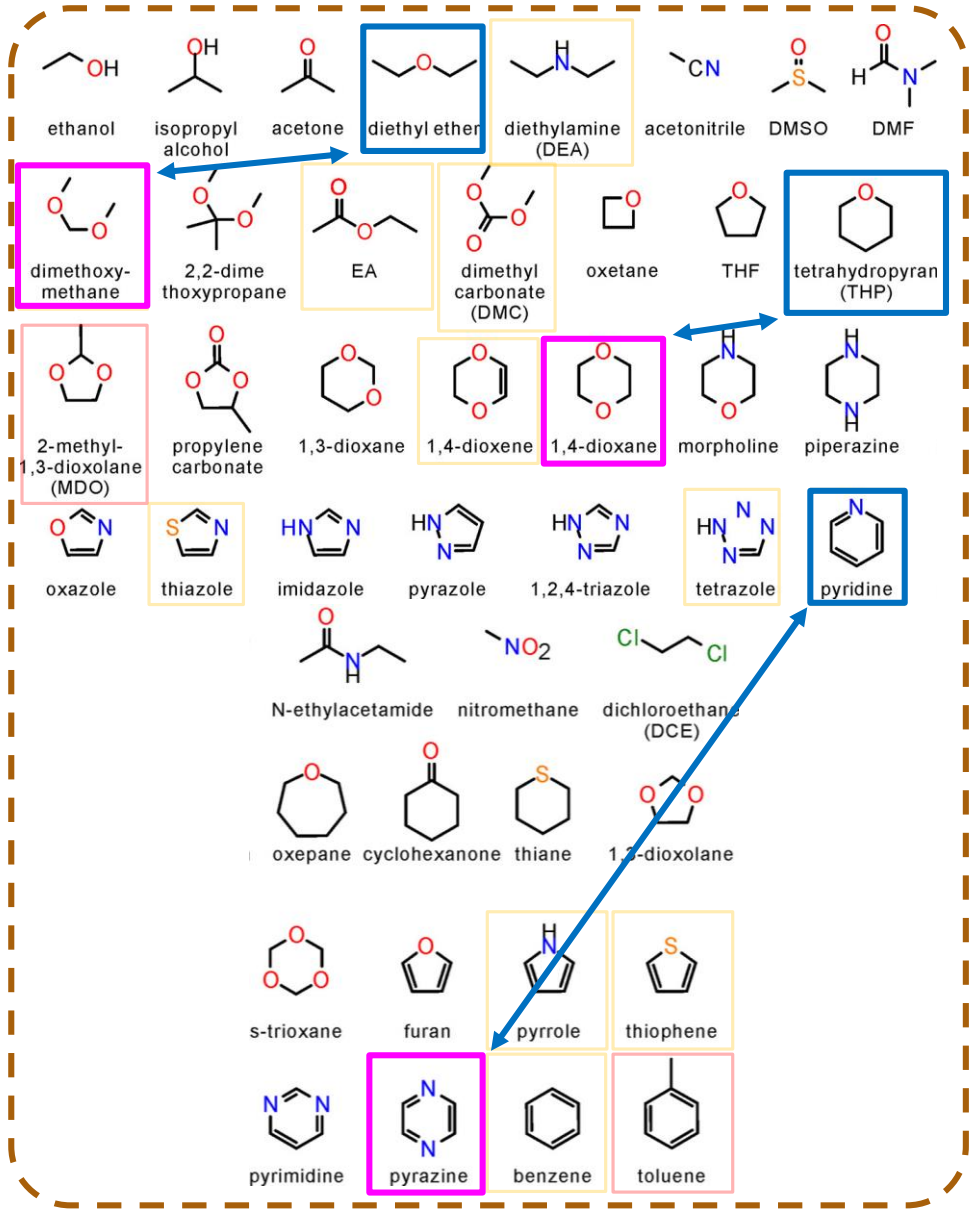
Difference of K_a between similar molecules



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toluene	141.22	0.08711	147.37	5.71×10^{-3}	2.73	0.36	65.49	9500 ± 1700[i]	9900 ± 1400[i]

Effect of solvent

	H_2O		$CHCl_3$
MDO	$22000 \pm 730\ M^{-1}$	→	$41 \pm 1\ M^{-1}$
1,4-dioxane	$14000 \pm 1500\ M^{-1}$	→	$62 \pm 1\ M^{-1}$
Pyrazine	$2200 \pm 38\ M^{-1}$	→	$11 \pm 1\ M^{-1}$
EA	$3400 \pm 24\ M^{-1}$	→	ND
DMC	$2300 \pm 110\ M^{-1}$	→	ND
Benzene	$1300 \pm 190\ M^{-1}$	→	ND

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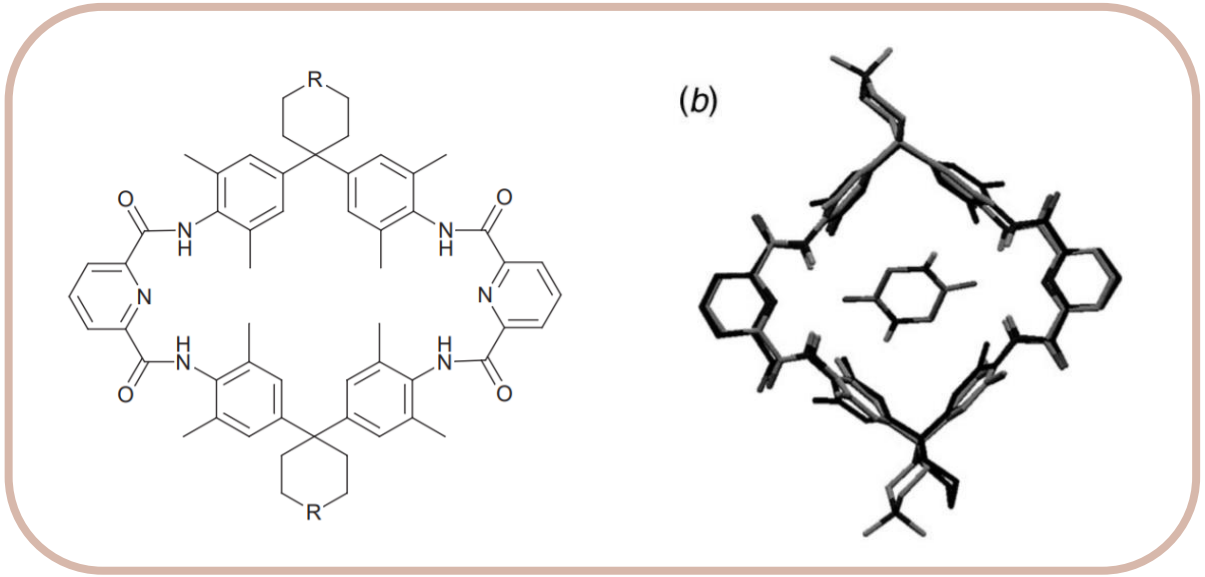
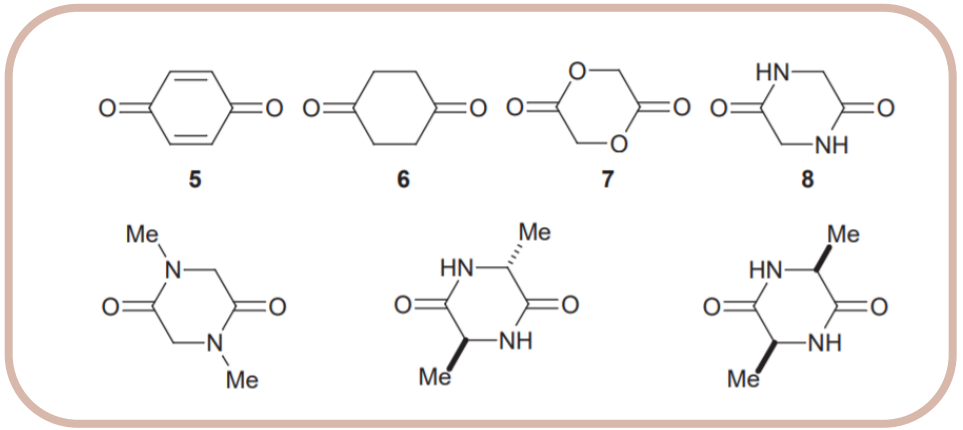
Effect of solvent

INormally, great decrease in affinity is observed when the solvent is changed from chloroform to water.

IWell-definedness of the cavity seems to be important.



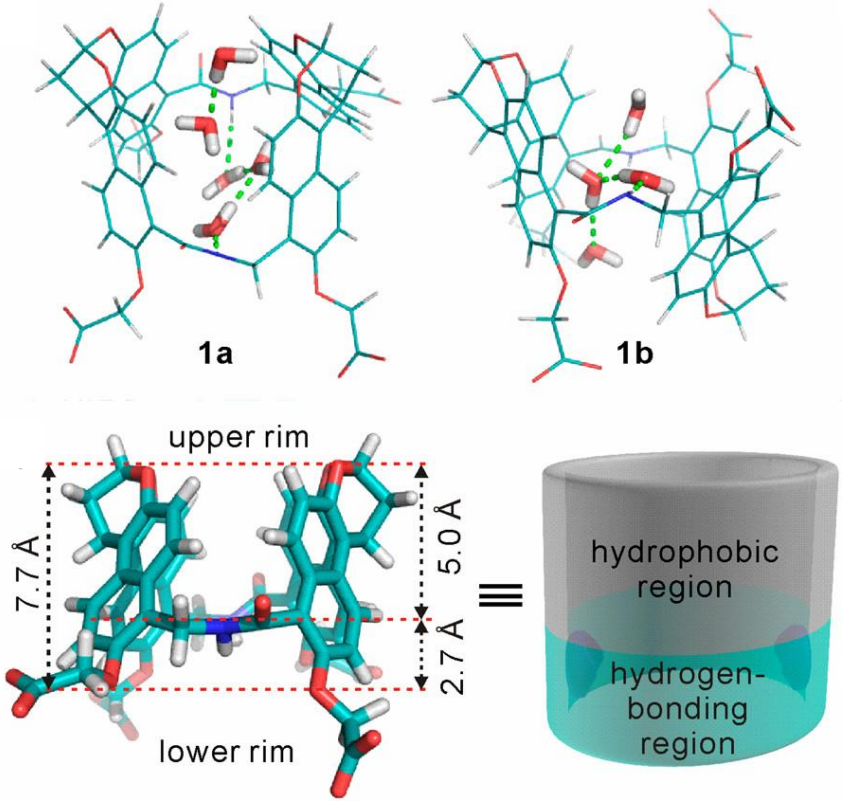
Host molecule



Guest molecule

Hydrophobic effect

- Average number of H-Bonding of cavity water is less then bulk water(3.6).
- Exclusion of cavity water (High energy water) is favorable in terms of enthalpy gain.

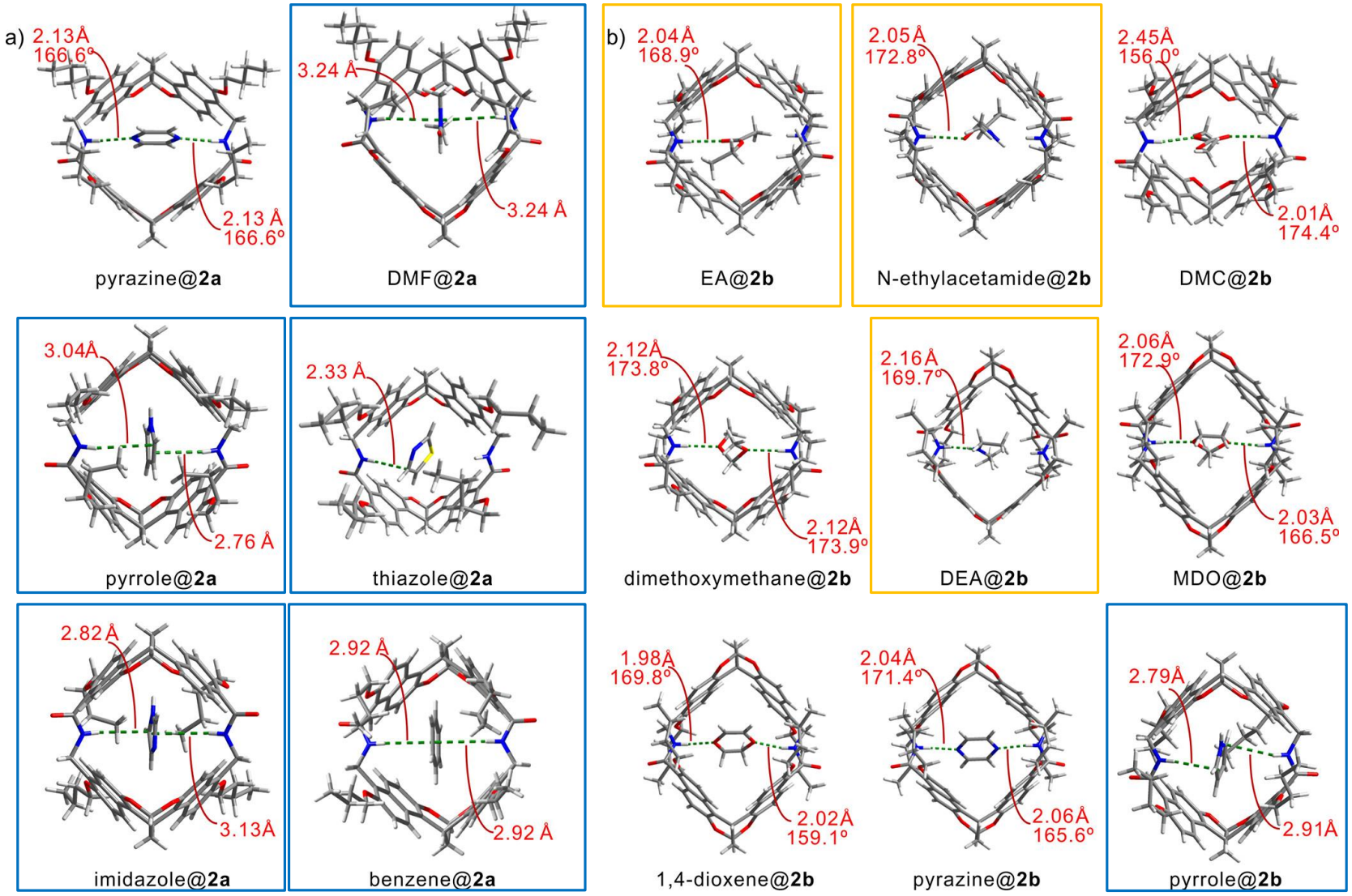


	1a			1b		
	N^b	m^c	PC^d	N^b	m^c	PC^d
hydrophobic region	1.5	1.67		2.3[e]	2.30	
hydrogen-bonding region	3.0	3.20 (2.80)[f]		1.5[e]	2.83 (1.77)[f]	
whole cavity	4.5	2.76	48%	3.8	2.67	35%

G Huang et al, *J. Am. Chem. Soc.*, **2016**, *138*, 14550.
H. Yao, et al., *J. Am. Chem. Soc.*, **2018,** *140*, 13466

Hydrogen bonding

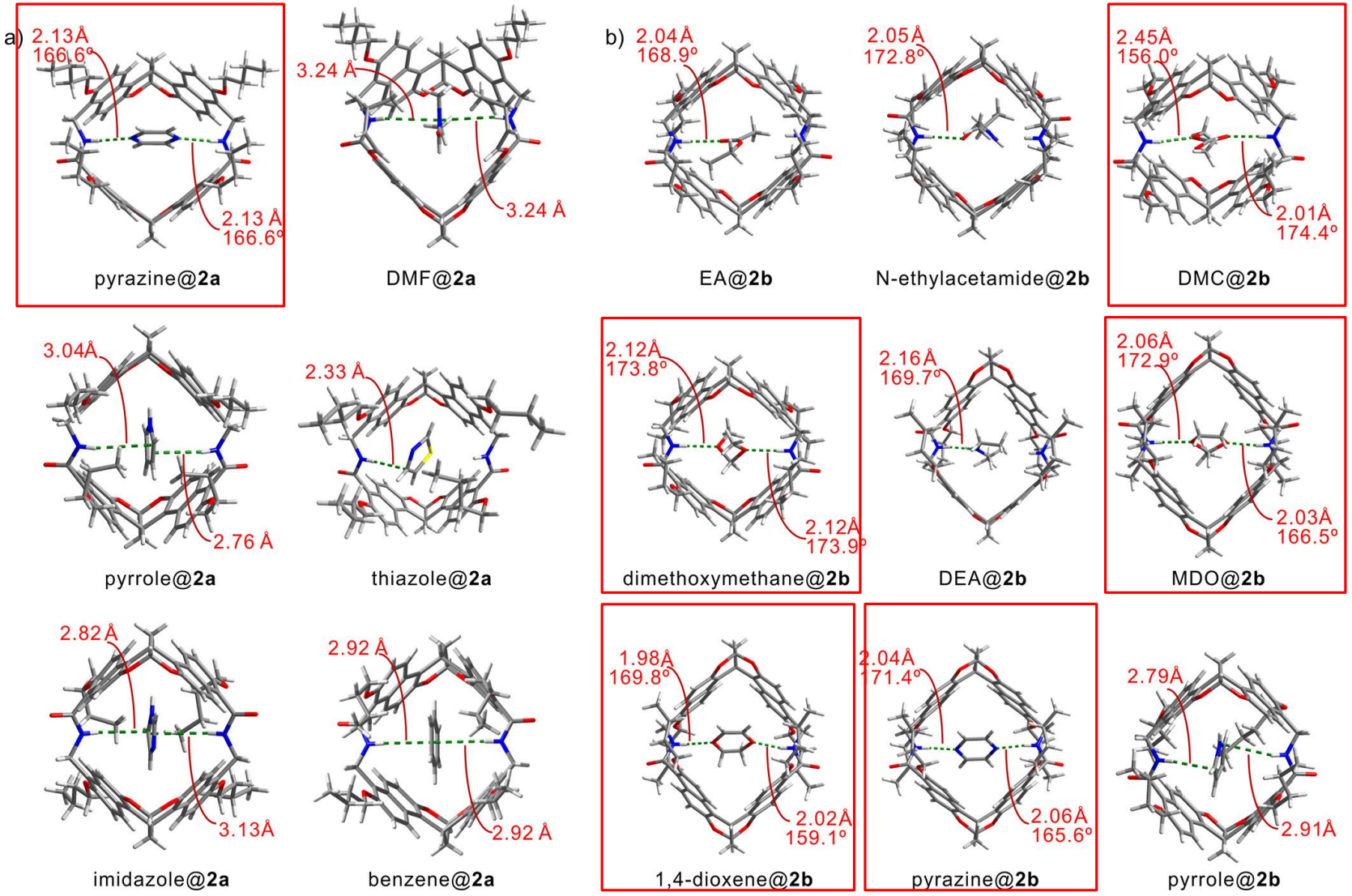
- Blue: H-bonding x1
- Yellow: NH-π



G Huang et al, *J. Am. Chem. Soc.*, **2016**, *138*, 14550.
H. Yao, et al., *J. Am. Chem. Soc.*, **2018,** *140*, 13466

Hydrogen bonding

- Red: H-bonding x2



G Huang et al, *J. Am. Chem. Soc.*, **2016**, *138*, 14550.
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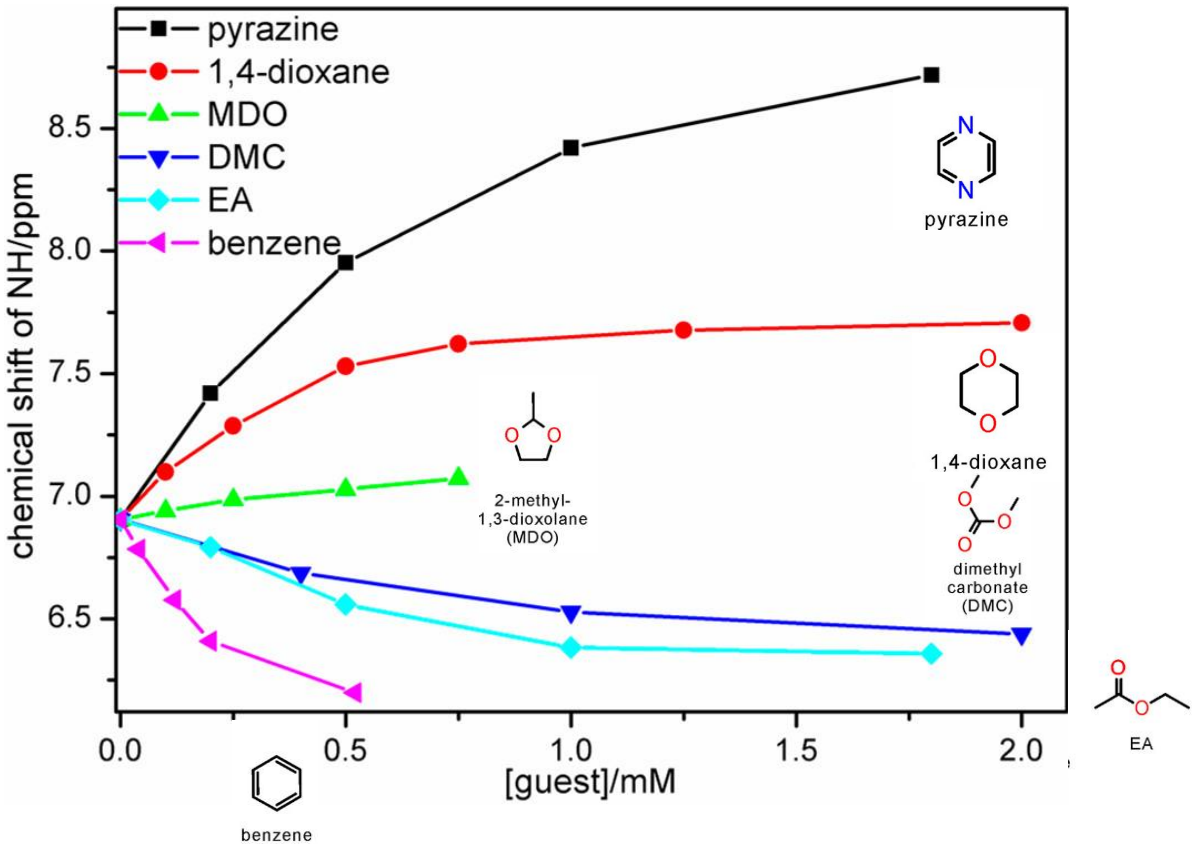
Hydrogen bonding

- Measured if host-gest hydrogen bond compensate for desolvation energy of the host.
- Complexation with Pyrazine, 1,4-diozane, MDO is favorable.
- Complexation with DMC, EA, benzene is disfavorable.
- Complexation with the later molecules is mainly driven by the exclusion of the cavity water.

NMR titration



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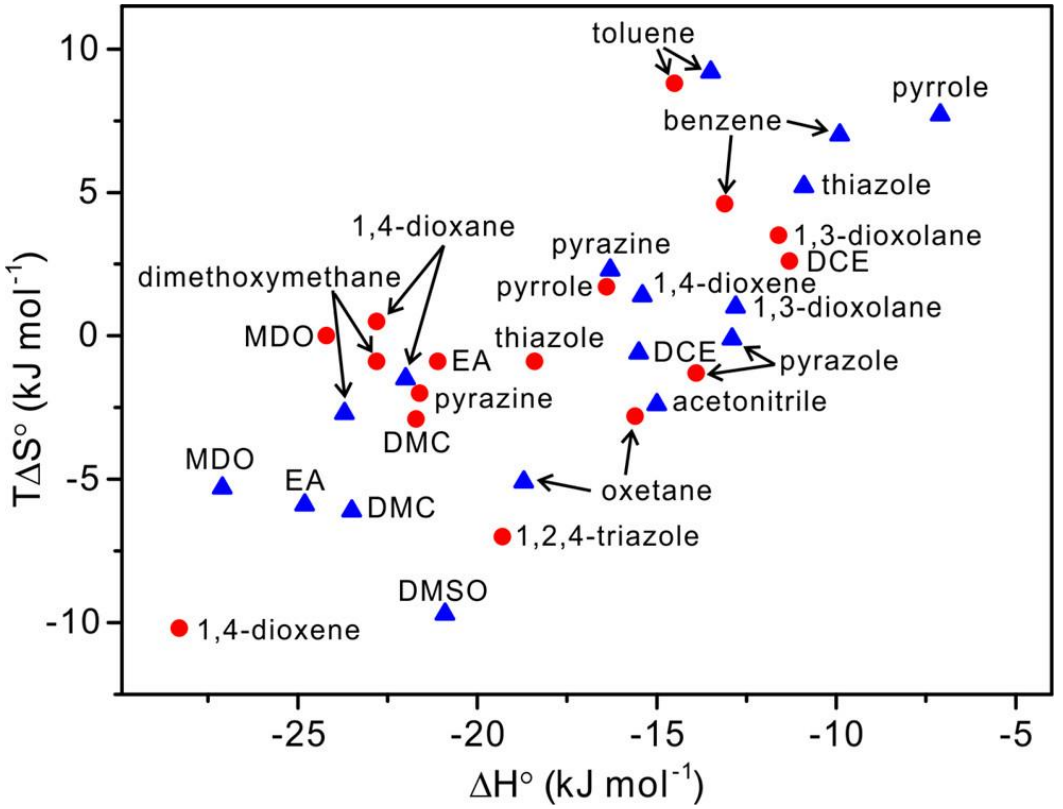
Entropy and enthalpy

- Weak entropy-enthalpy compensation was observed.
- Roughly speaking, enthalpy but not entropy is the major driving force for the complexation.



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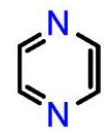
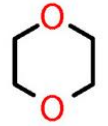
The criteria for good guest molecules

1.Good guest should be able to form hydrogen bond with the host.

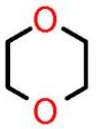


pyrazine

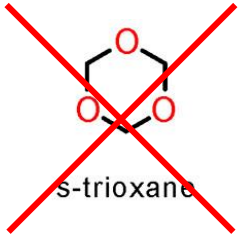


1,4-dioxane

2.Good guest should not have additional hydrogen bond acceptor.

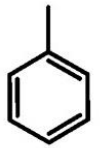


1,4-dioxane



s-trioxane

3. Good guest should have large enough hydrophobic group in order to expel the cavity waters.


toluene

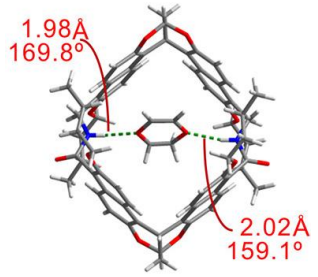
>


benzene

G Huang et al, *J. Am. Chem. Soc.*, **2016**, *138*, 14550.
H. Yao, et al., *J. Am. Chem. Soc.*, **2018,** *140*, 13466

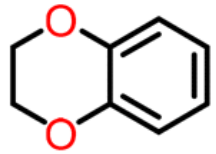
More strong affinity?

- It is expected that if the guest could expel more water, the affinity will be stronger.
- Combining complexation driven by hydrophobic effect and specific binding by H-bonding, interaction will be stronger and more selective.



1,4-dioxene@**2b**

Table 4. Association Constants K_a (M^{-1}) and Thermodynamic Parameters ($\Delta G°$, $\Delta H°$, and $-T\Delta S°$; kJ mol^{-1}) of Molecular Tubes 1a and 1b with 3 and 4 in H_2O at 25 °C as Determined by Fluorescence (FL) and ITC Titrations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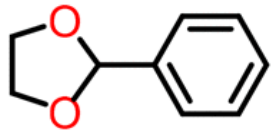
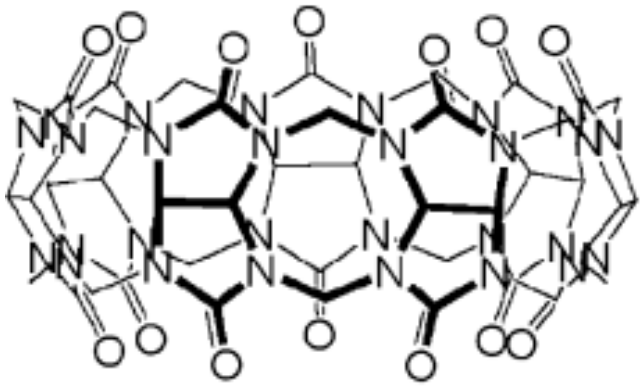

4

		FL	ITC			
		$K_a \times 10^4$	$K_a \times 10^4$	$\Delta G°$	$\Delta H°$	$-T\Delta S°$
3	1a	1.6 ± 0.3	1.1 ± 0.1	−23.1	−38.8	15.7
	1b	2.9 ± 0.1	1.3 ± 0.1	−23.5	−38.7	15.2
4	1a	220 ± 18	140 ± 0.1	−35.2	−45.1	9.9
	1b	51 ± 0.1	46 ± 2.7	−32.4	−52.7	20.3

G Huang et al, *J. Am. Chem. Soc.*, **2016**, *138*, 14550.
H. Yao, et al., *J. Am. Chem. Soc.*, **2018,** *140*, 13466

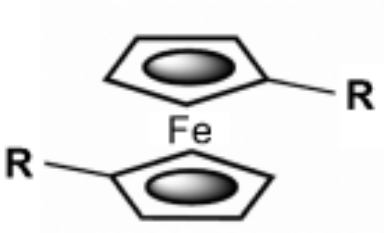
General tendency

- Complexation of a hydrophobic cavity and the guest molecule tends to be driven by a gain of enthalpy.



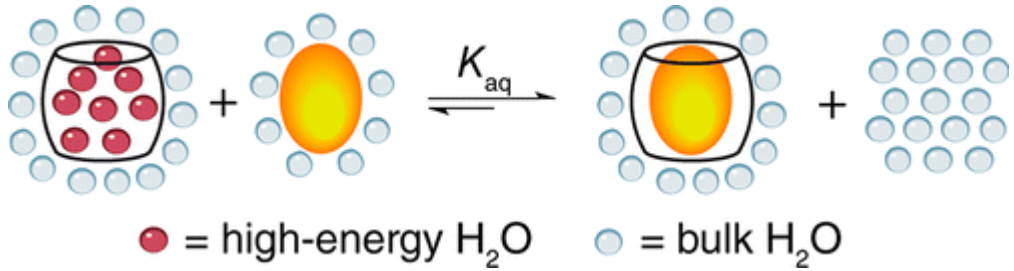
Cucurbit[7]uril

ΔG = 90 kJ mol^{-1}, $T\Delta S$ = –2 kJ mol^{-1}



Ferrocene, R = $CH_2{}^+NMe_3$

cf. Biotin-Avidin: ΔG = 90 kJ mol^{-1}



1. Introduction

2. Analysis on molecular recognition in water

3. Case examples

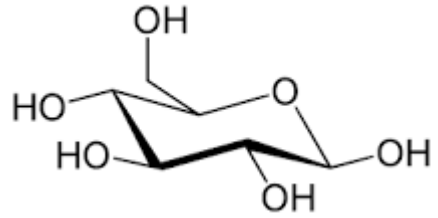
    Recognition of glucose in water

    Recognition of lysine in water

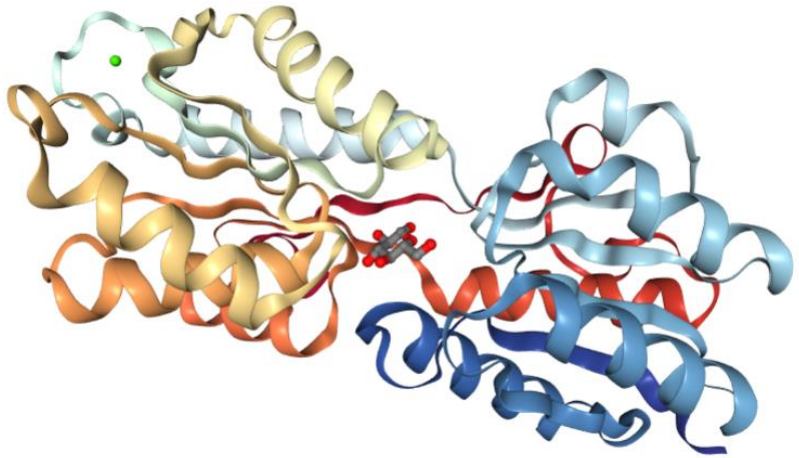
4. Appendix

Recognition of glucose

- Sugar is a typical hydrophilic molecule.
- Sugar is crucial element for organisms.
- Recognition of sugar is challenging not only for synthetic hosts, but also for biomolecules.
- Periplasmic GBP, which has the highest affinity, bind to glucose in 5×10^6 M^{-1} affinity.
- Other typical lectins have weaker affinity.



β-glucose



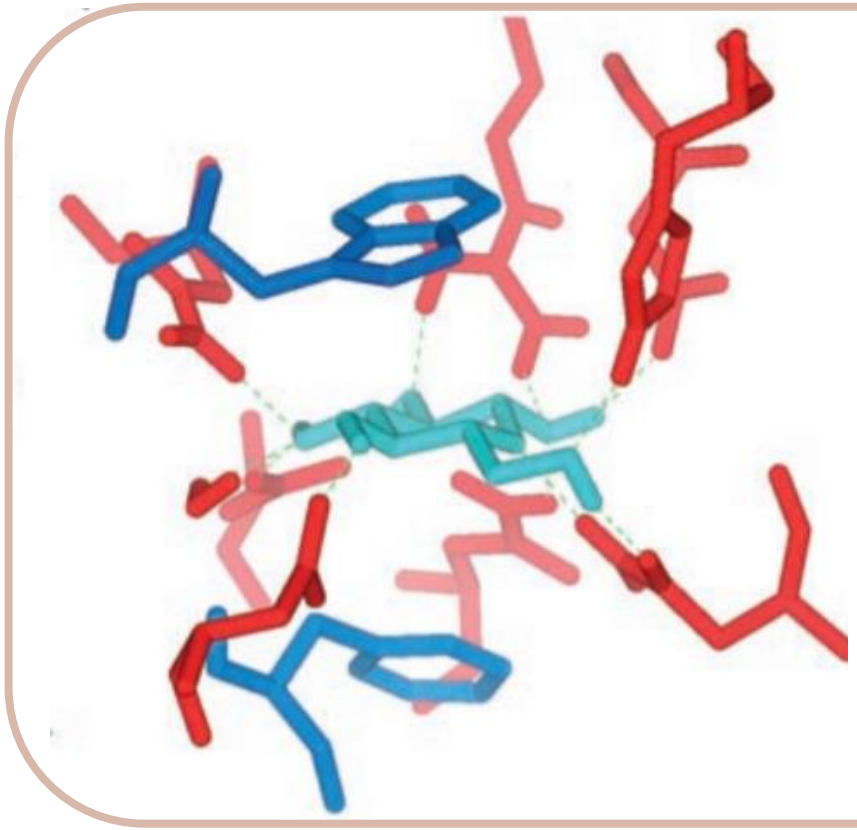
glucose/galactose binding protein (E.coli)

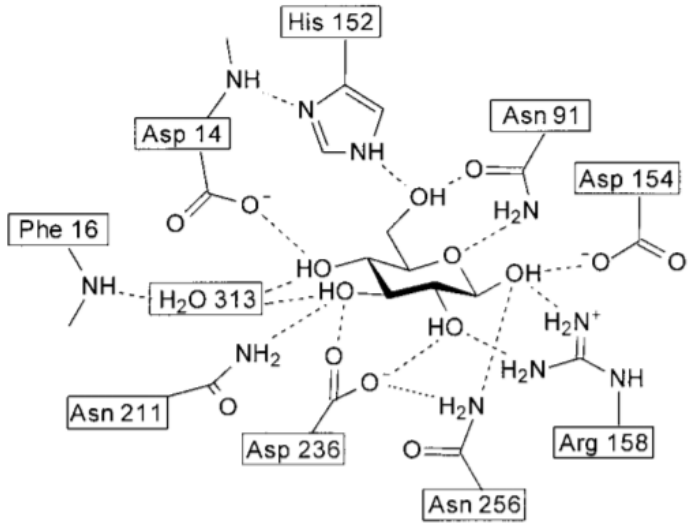
PDB : 2HPH

E. Klein et al, *Angew. Chem. Int. Ed.*, **2008,** *47*, 2693

Recognition of glucose

- In 1998, A.P.Davis and coworkers synthesized synthetic glucose receptor, mimicking the binding site of E.coli periplasmic GBP.

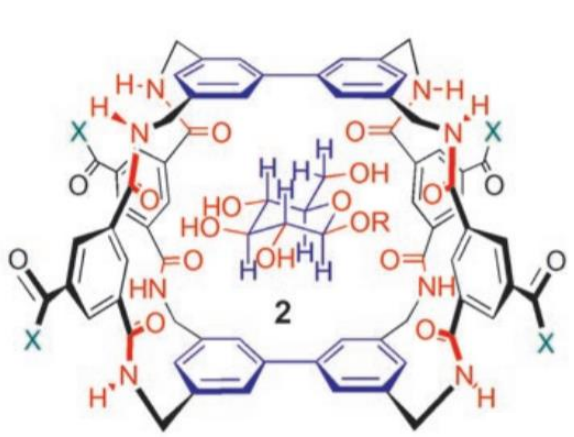


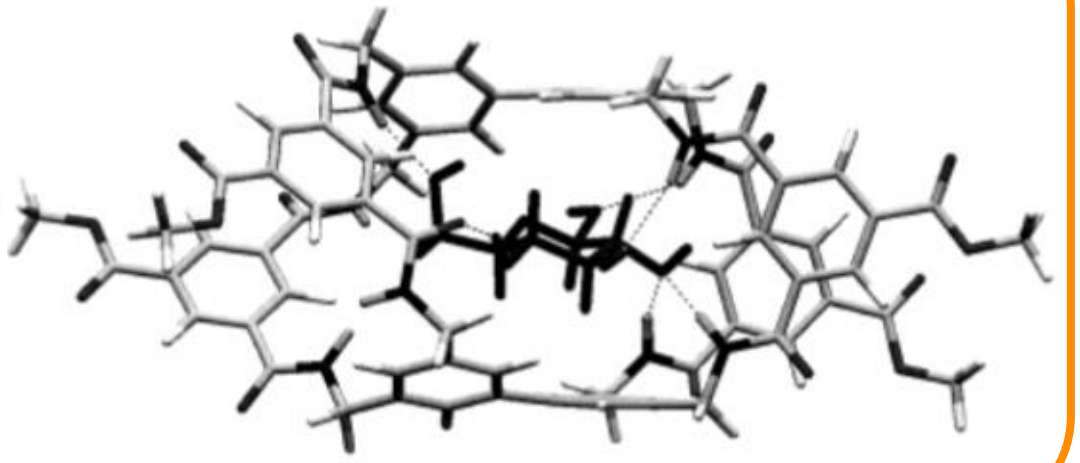


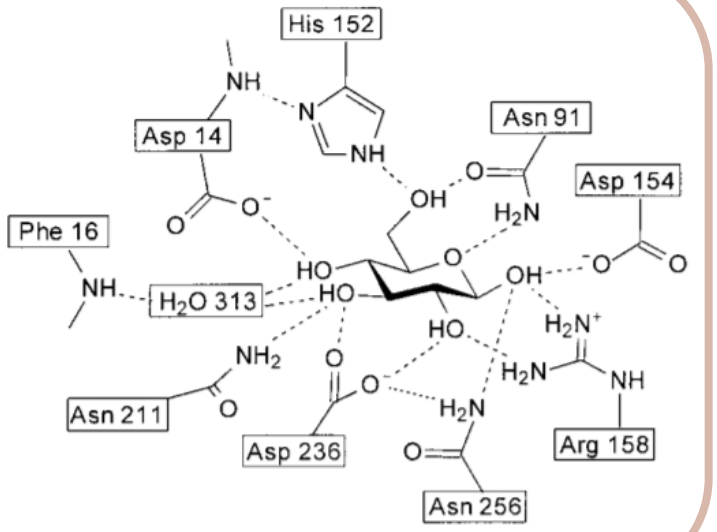
A.P.Davis et al., *Angew. Chem. Int. Ed.*, **1998**,37, 2270
E. Klein et al, *Angew. Chem. Int. Ed.*, **2008,** *47*, 2693

Recognition of glucose

IH-bond between the N-H proton and the O atom of the glucose is responsible for the recognition.



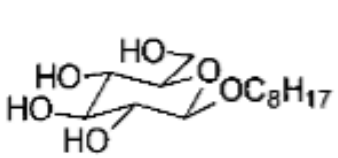




A.P.Davis et al., *Angew. Chem. Int. Ed.*, **1998**,37, 2270
E. Klein et al, *Angew. Chem. Int. Ed.*, **2008,** *47*, 2693

Recognition of glucose

IThe affinity was maintained even in the presence of 8% of MeOH.



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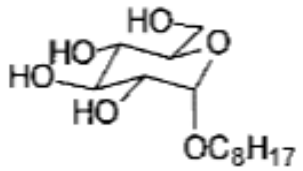

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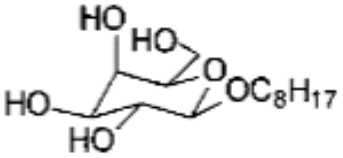


7

In $CHCl_3$

Table 2. Results from fluorescence titrations of **1** with octyl pyranosides **5**–**7**[a]

Pyranoside	K_a [M^{-1}][b]	$-\Delta G^\circ$ [kJ mol^{-1}]	$-\Delta I$ [%][c]
5	300000 (±6%)	30.7	36.4
6	13000 (±8%)	23.1	18.8
7	110000 (±12%)	28.3	22.8

In $CHCl_3$(8% MeOH)

Table 1. Results from ^{1}H NMR titrations of **1** with octyl pyranosides **5**–**7**[a]

Pyranoside	K_a [M^{-1}]	$-\Delta G^\circ$ [kJ mol^{-1}]	$\Delta\delta$ [ppm][b]
5	980 (±2%)	17.4	0.32
6	20 (±23%)	7.8	0.30
7	220 (±5%)	13.6	0.27

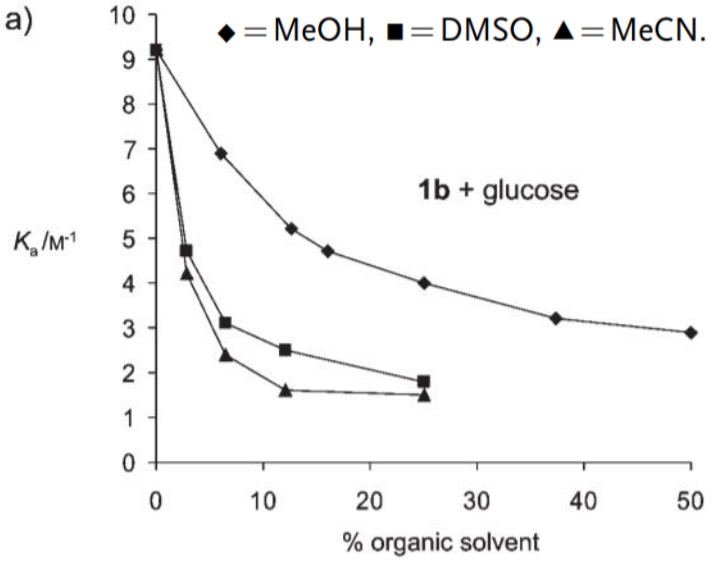
A.P.Davis et al., *Angew. Chem. Int. Ed.*, **1998**,37, 2270

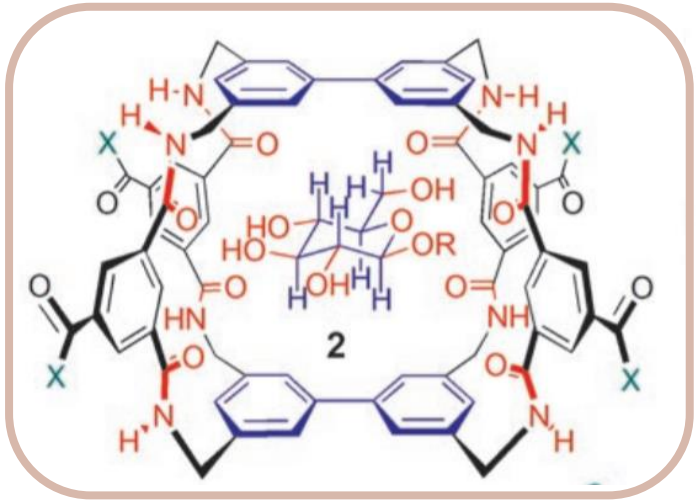
Recognition of glucose

- In H_2O, glucose, binding constant was 9 M^{-1}
- The affinity was depleted by the addition of organic solvents.
- The effect was in order of

  MeOH < DMSO < MeCN

- Involvement of hydrophobic effect is suggested.

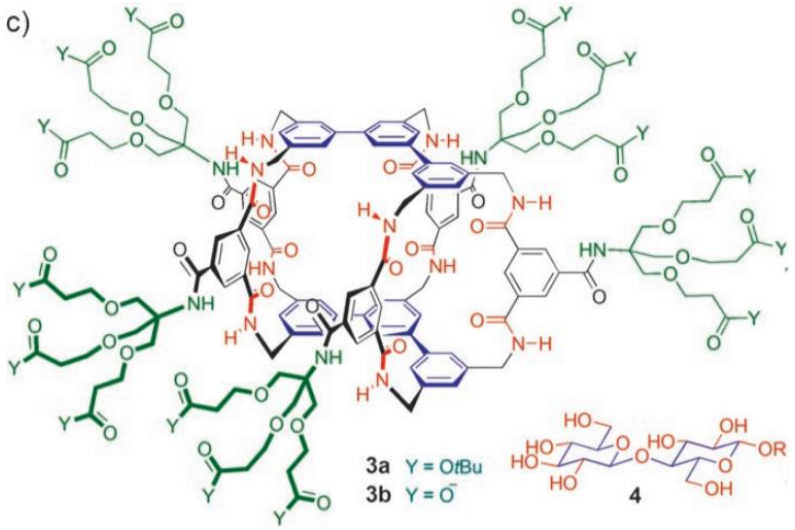


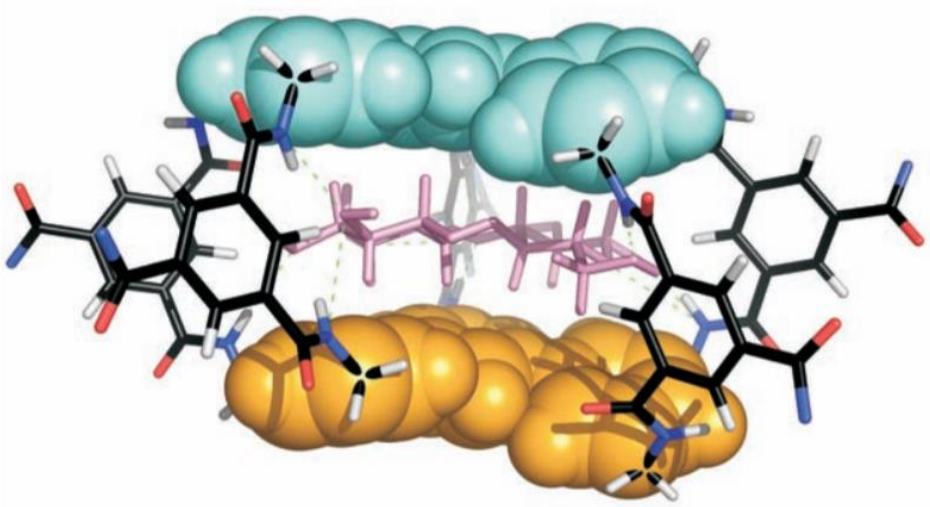


E. Klein et al, *Angew. Chem. Int. Ed.*, **2008,** *47*, 2693

Recognition of glucose

- New host molecule for cellobiose was synthesized by Davis's group in 2007.
- The new molecule maintained the binding affinity even in the pure water.
- In D_2O: 600 M^{-1}

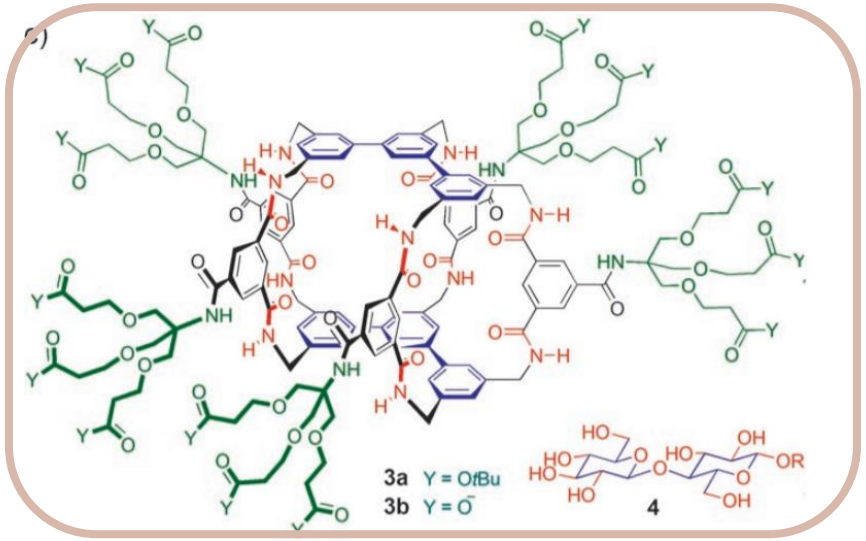




Y.Ferrand et al., *Science*, **2007**, *318*, 619
E. Klein et al, *Angew. Chem. Int. Ed.*, **2008,** *47*, 2693

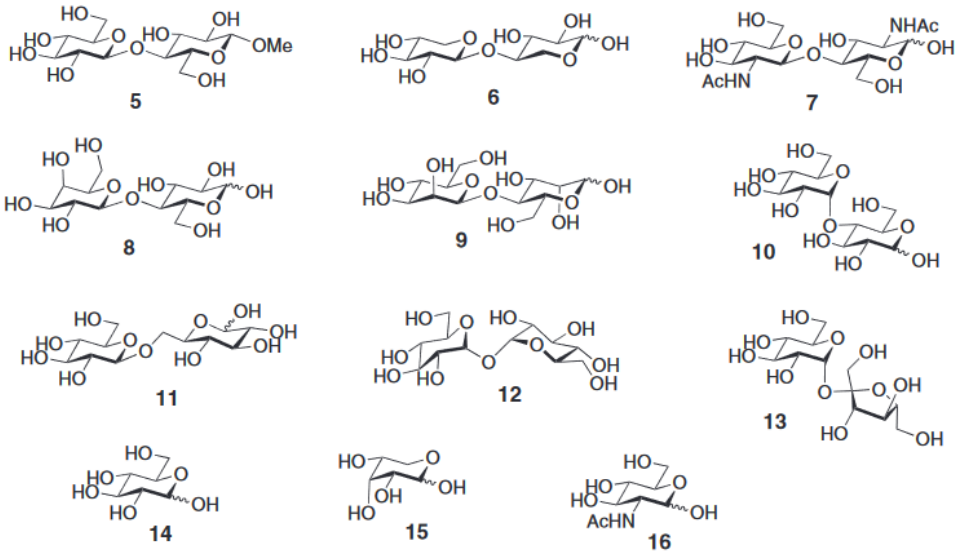
Recognition of glucose

- Methyl β-D-cellobioside had the strongest affinity.
- D-Xylobiose which has very similar structure had the affinity of 250.
- The other substrate had very weak affinity.



Carbohydrate	K_a (M^{-1})		
	^{1}H NMR	ICD	Fluorescence
D-Cellobiose (**4**, 1β–OH:1α–OH = 3:2)	600*§	580	560
Methyl β-D-cellobioside (**5**)	‡	910	850
D-Xylobiose (**6**)	‡	250	270
D-*N,N'*-diacetylchitobiose (**7**)	120*	ND	120
D-Lactose (**8**)	‡	11	14
D-Mannobiose (**9**)	‡	13	9
D-Maltose (**10**)	‡	15	11
D-Gentiobiose (**11**)	ND	12	5
D-Trehalose (**12**)	||	||	ND
D-Sucrose (**13**)	ND	||	||
D-Glucose (**14**)	11†§	12	||
D-Ribose (**15**)	ND	||	||
D-*N*-acetylglucosamine (**16**)	24†	ND	19

*Slow exchange on the NMR time scale. †Fast exchange on the NMR time scale. ‡Intermediate exchange (leading to broad peaks and preventing the determination of K_a). §T = 278 K. ||No change in spectrum upon addition of carbohydrate.



Y.Ferrand et al., *Science*, **2007**, *318*, 619
E. Klein et al, *Angew. Chem. Int. Ed.*, **2008,** *47*, 2693

Recognition of glucose

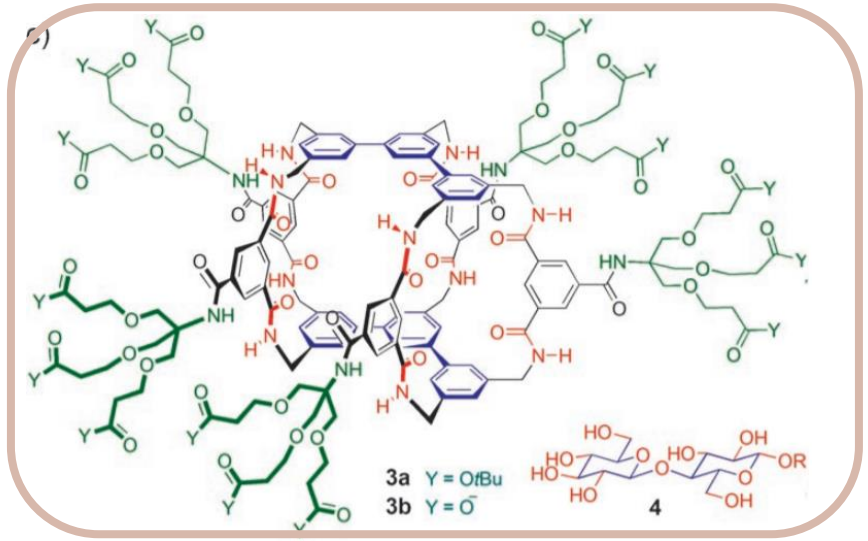
IThe affinity was depleted by the addition of organic solvents.

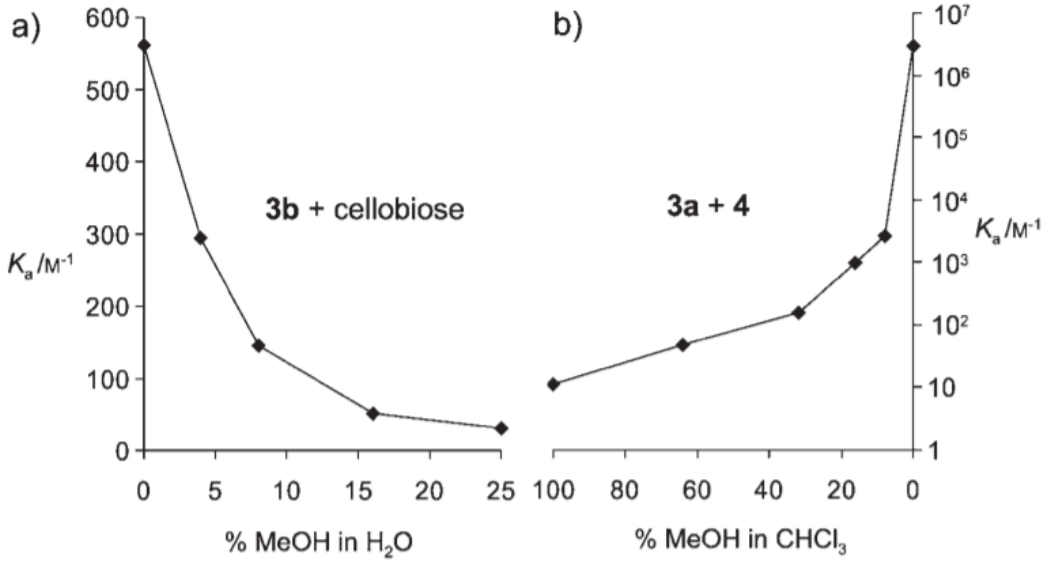
IThe effect was in order of

MeOH < DMSO < MeCN

IThe sensitivity for organic solvent was stronger than the previous host molecule.

IInvolvement of hydrophobic effect is suggested.

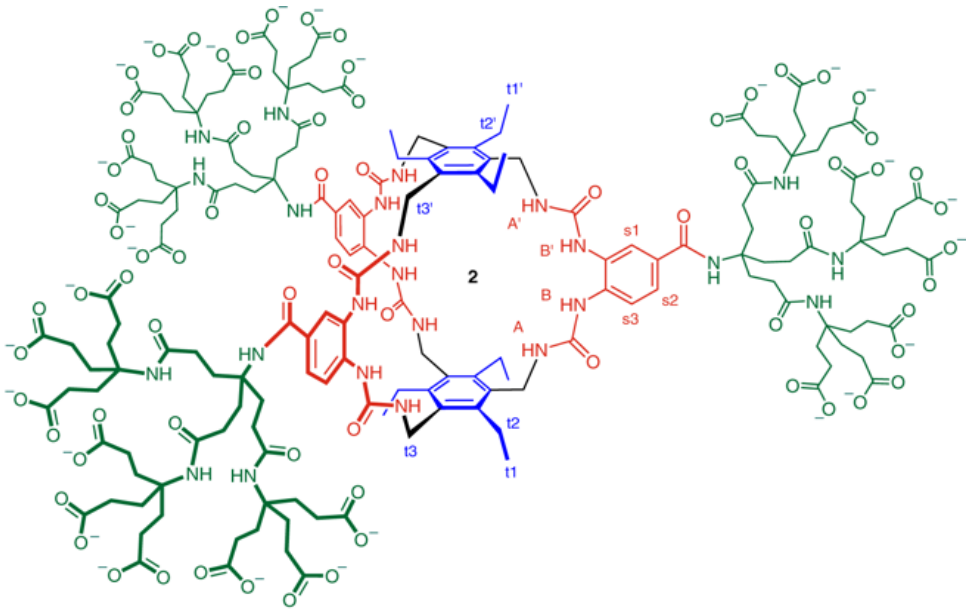


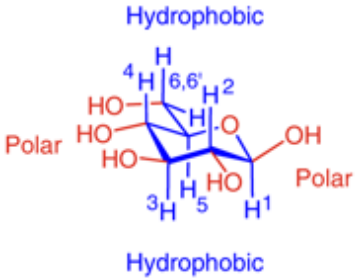


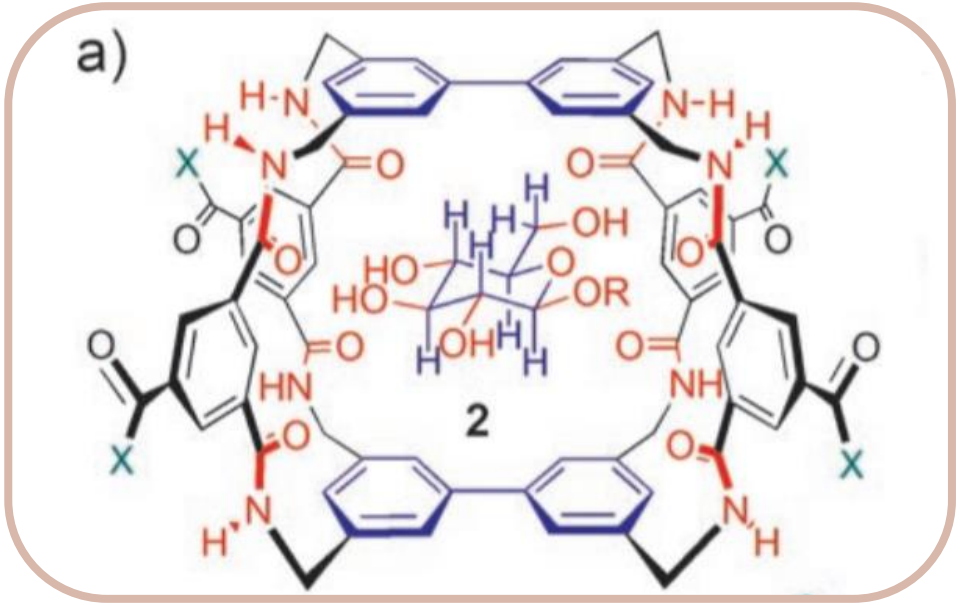
Y.Ferrand et al., *Science*, **2007**, *318*, 619
E. Klein et al, *Angew. Chem. Int. Ed.*, **2008,** *47*, 2693

Recognition of glucose

- Latest host molecule could bind glucose in a biomolecule compatible affinity and selectivity. (In H_2O : 1.8×10^4 M^{-1})
- Comparing with the first molecule, the well-definedness of the cavity seems to be improved.



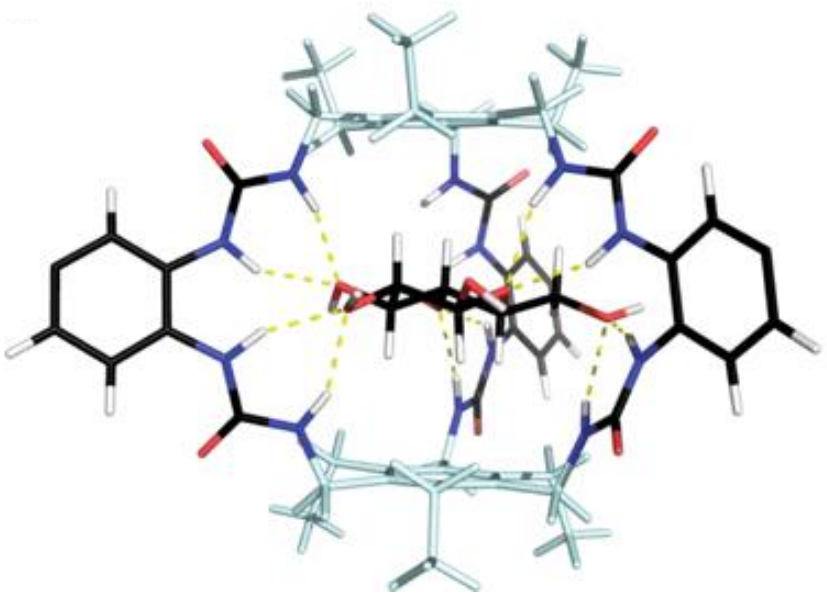


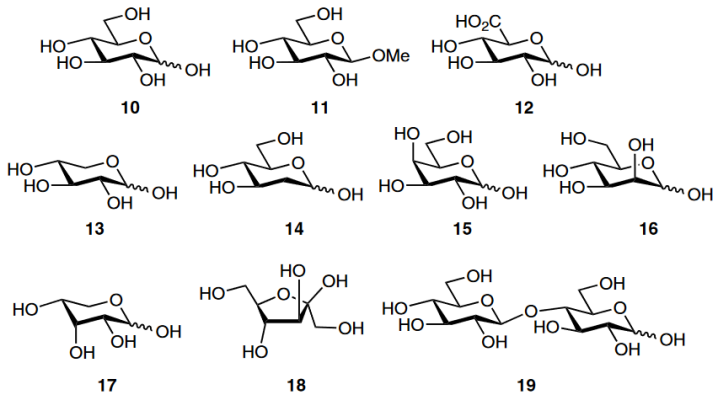


Introduction

- Most other saccharides bound approximately 100 times weaker.

c.f. : lectin ConcanacalinA : 500 M^{-1} , also bind to mannose.





Substrate	K_a (M^{-1})	
	NMR	ITC
D-Glucose **10**	18,600	18,200
Methyl β-D-glucoside **11**	7,500	7,900
D-Glucuronic acid **12**	ND	5,300
D-Xylose **13**	ND	5,800
2-Deoxy-D-glucose **14**	ND	725
D-Galactose **15**	130	180
D-Mannose **16**	140	140
D-Ribose **17**	270	220
D-Fructose **18**	51	60
D-Cellobiose **19**	31	30

Nat. Chem., **2019,** *11*, 52

1. Introduction

2. Analysis on molecular recognition in water

3. Case examples

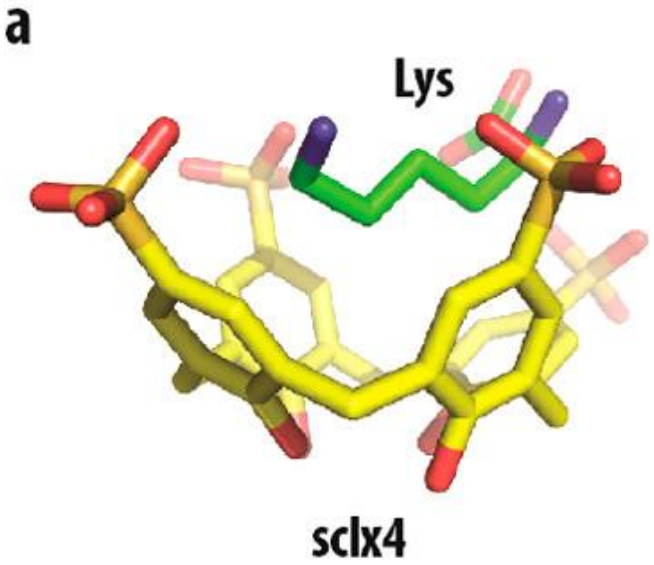
   Recognition of glucose in water

   Recognition of lysine in water

4. Appendix

Recognition of Lysine in water

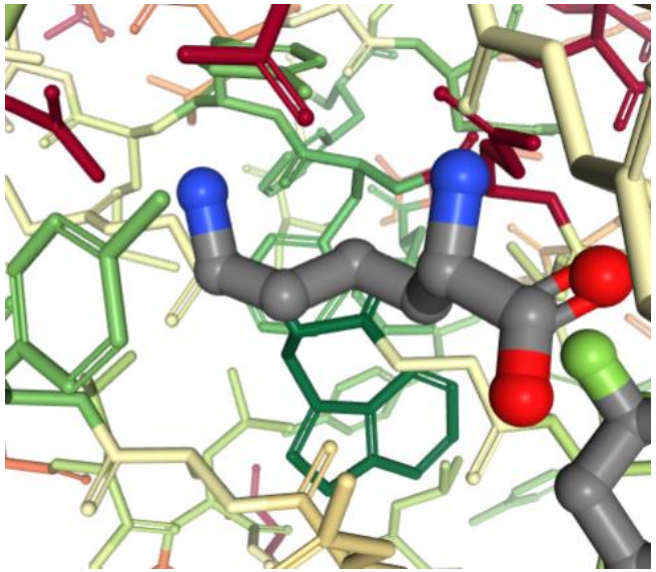
- 4-Sulfocalix[4]arene is used for the recognition of Lysine.
- They form 1:1 complex in water.
- K_D=600
- Methylated lysine binds stronger.



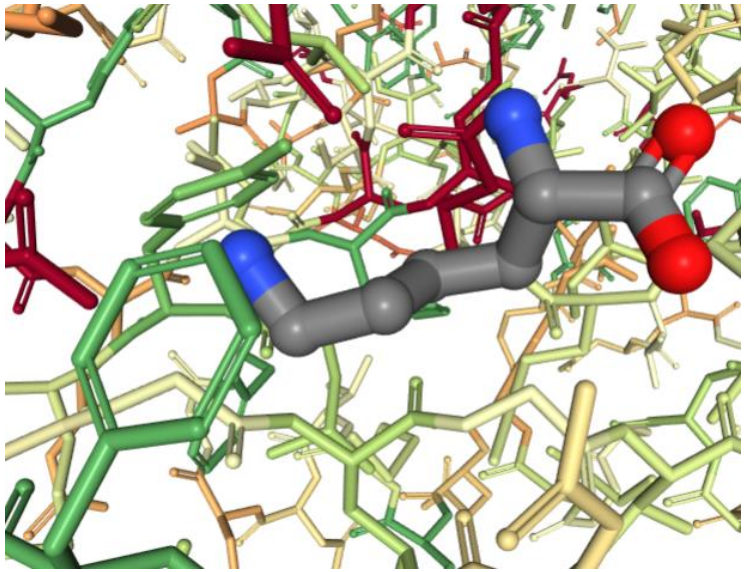
Sam van Dun et al., *J. Am. Chem. Soc.*, **2017,** *139*, 13960
M. Selkti et al., *Chem. Commun.*, **2000**, *161*

Recognition of Lysine in water

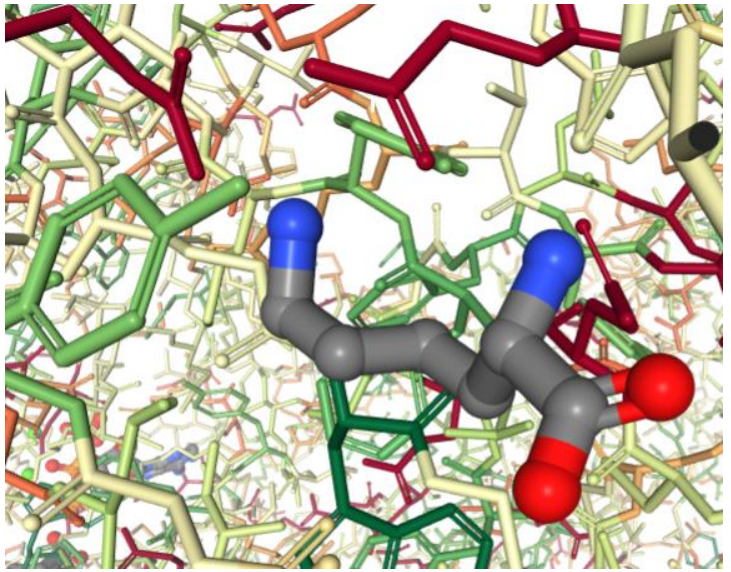
- Aromatic AA and Acidic AA around the Lys binding site is conserved in Lysyl-tRNA synthetase.



Cryptosporidium parvam



E.coli



Human

PDB : 3BJU, 1BBU, 6HCW

Summery

- Understanding the molecular recognition of hydrophilic molecules in water is important for many fields.
- Combining the complexation by the hydrophobic effect and the recognition by H-bonding is the basic strategy for the molecular recognition in water.
- This is also seen in biomolecules.

1. Introduction

2. Analysis on molecular recognition in water

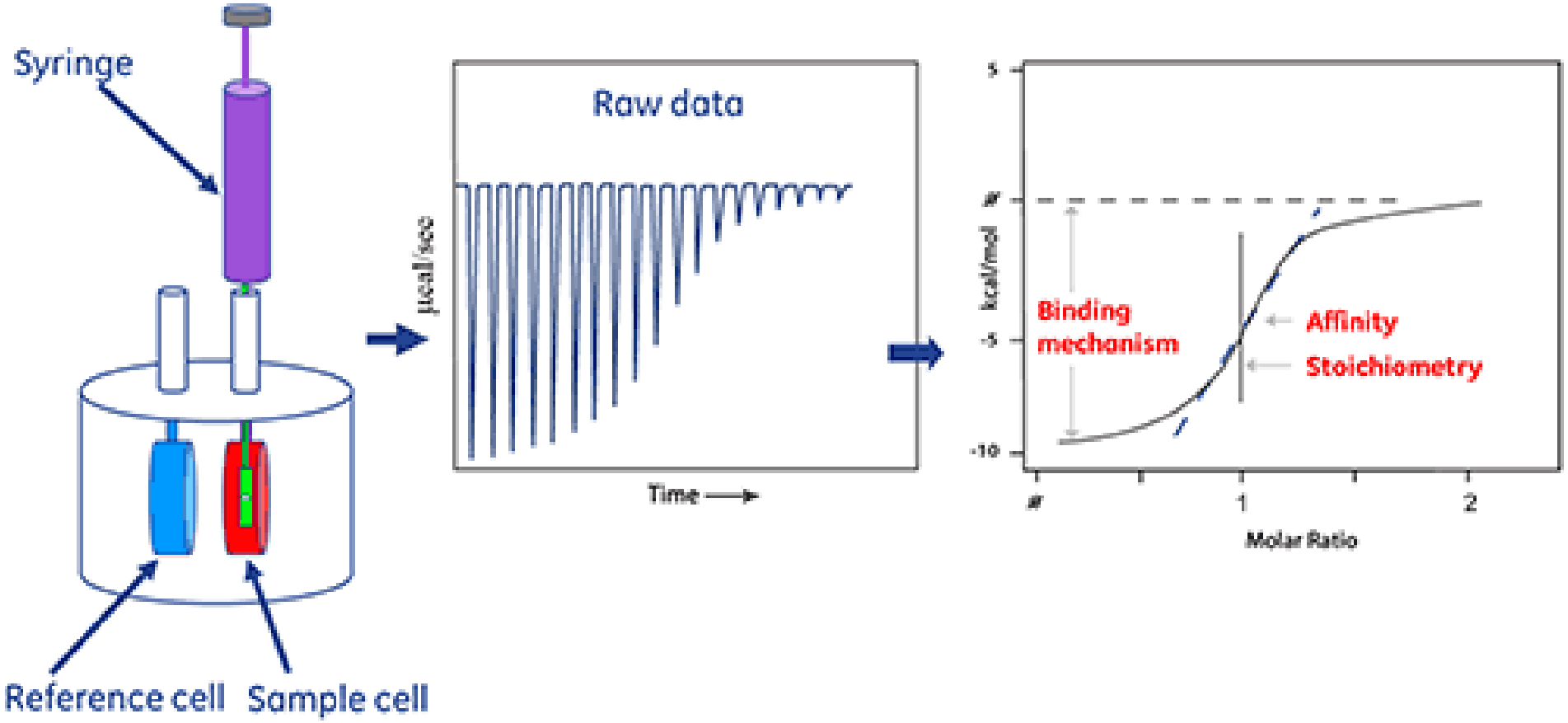
3. Case examples

    Recognition of glucose in water

    Recognition of lysine in water

4. Appendix

Appendix : ITC



https://www.malvernpanalytical.com/jp/products/technology/microcalorimetry/isothermal-titration-calorimetry